



Understanding pH and Osmolarity

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Advancing the Science of Infusion Therapy



Outline

- pH and osmolarity tolerance guidelines,
- Definitions of pH and osmolarity,
- pH and osmolarity in vitro data,
- pH and osmolarity of common infusions,
- Altering pH and osmolarity, and
- Pharmacists' perspective on pH and osmolarity.

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Scope of this presentation

- Clinical and pharmaceutical aspects of pH and osmolarity of infusates.
 - Damage induced by ions (pH) and osmolarity rarely occurs as an isolated event.
 - Other factors: mechanical, material, duration, infection, particulate, and chemical



INS Standard

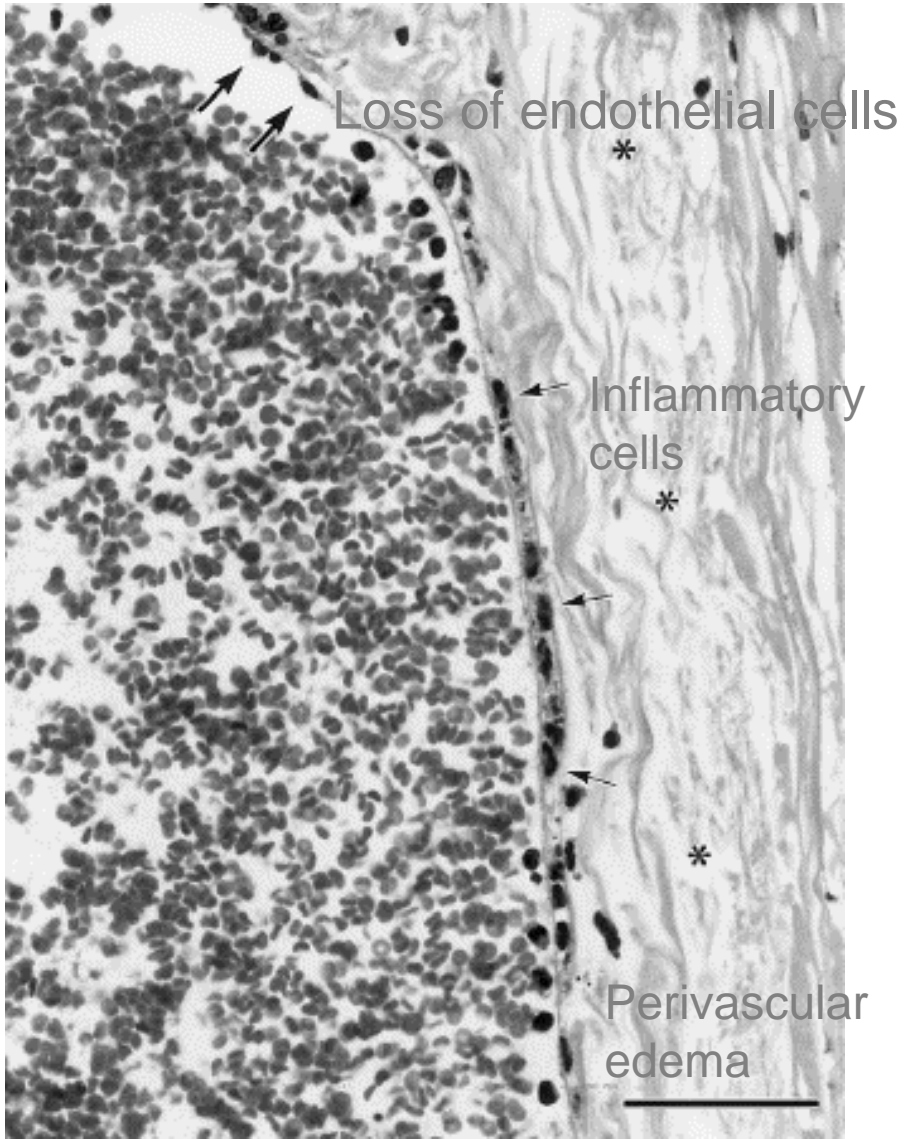
- To prevent or reduce vascular complications, INS standards recommend that
 - Infusions with a pH outside the range of 5 to 9 and/or
 - an osmolarity greater than 600
 - be administered through an access device that delivers the infusate into a blood vessel with a high rate of blood flow.

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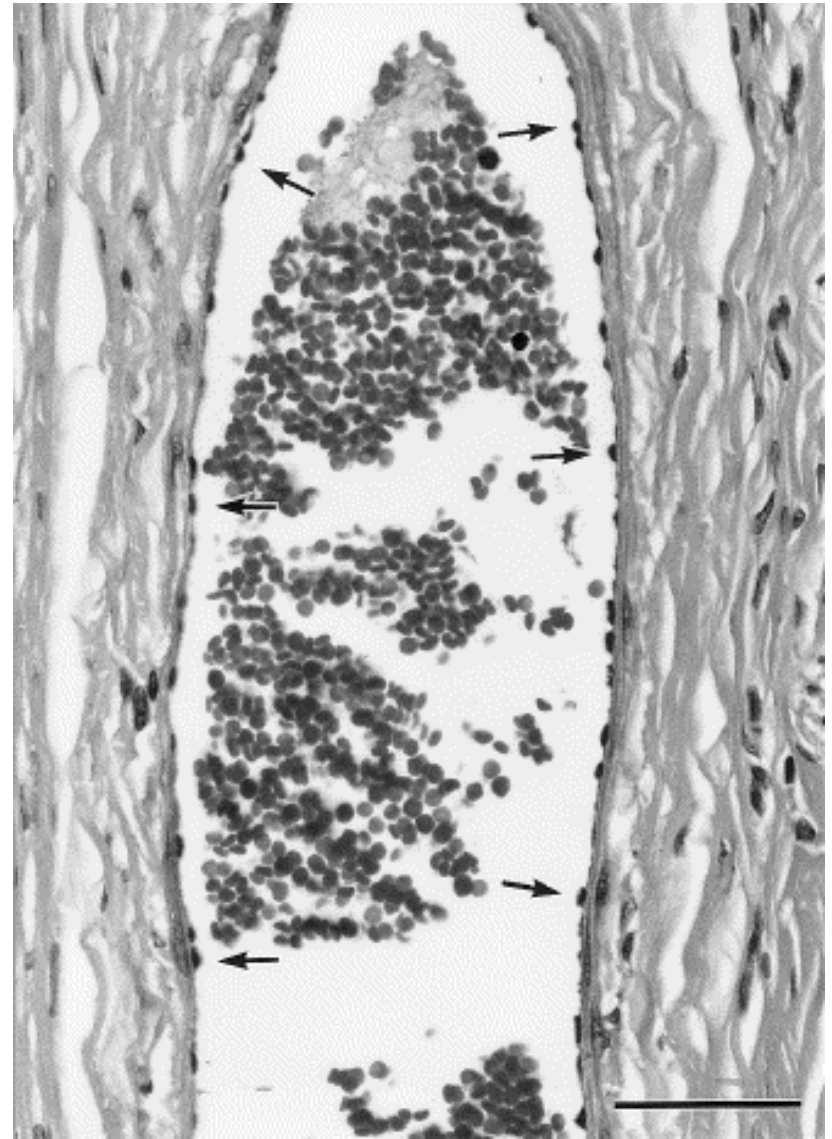


Histopathological changes

- Chemical irritation causes:
 - Loss of venous endothelial cells,
 - Inflammatory cell infiltration,
 - Edema
 - Thrombus
 - Proximal and distal to the catheter tip.



Damaged



Intact



Review of osmolarity and pH

- Osmosis/osmolality.
 - human plasma osmolality is 290 mOsm/L (285 - 310 mOsm/L).
- Isotonic - Normal Saline
- Hypotonic - $\frac{1}{2}$ Normal Saline
- Hypertonic - Dextrose 5% & Normal Saline



Review of osmolality and pH

- Osmolality and osmolarity
 - Osmolality is defined as the number of milliosmoles per kilogram of solvent.
 - Osmolarity is defined as the number of milliosmoles per liter of solution.
- Intravenous fluid labeling has osmolarity, but not required for intravenous admixtures



Review of osmolality and pH

- Osmolality can be estimated from:
 - Osmolality = $[(C_i E_i) \times 0.58/1.86] \times 1000$ where C = grams of solute per 100ml of solution, E = the sodium chloride equivalent, and $(C_i E_i)$ = the sum of the products of $(C \times E)$ for each solute in the solution.
 - NaCl Equivalent Value tables exist for common drugs
 - When the sodium chloride equivalents are unknown, the following equation is used to determine a value for E: $E = 17 \times (\text{Liso}/\text{MW})$ where Liso 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 Liso value of 4.3 is used for disodium salts and a value of 3.4 for all other drugs.



Review of osmolarity and pH

- Osmolarity can be determined from the formula
 - $$\text{mOsM} = \frac{\text{wt of substance (g/L)}}{\text{molecular wt (g)}} \times \text{number of specie (ion)} \times 1000$$
 - Molecular wt from package insert
 - As the concentration of the solute increases, interaction among solute particles increases and actual osmolar values decrease when compared to ideal values. The variance can be significant for concentrated solutions.
 - Calculated osmolarity 0.9% NaCl = $9/58.4 \times 2 \times 1000 = 308$
 - Measured osmolality 0.9% NaCl = 286



Review of osmolarity and pH

- pH
 - The pH scale runs from 0 to 14
 - Logarithmic scale, based on power of 10
 - 1 pH unit change equals a 10-fold change in H⁺ ion concentration
 - Change from pH 7.35 to pH 7.15 is a 2% drop in pH but equals a 24% change in H⁺ ion concentration.



Review of osmolarity and pH

Common acids and bases:

	[H ⁺]	pH	Example
Acids	1 X 10 ⁰	0	HCl
	1 x 10 ⁻¹	1	Stomach acid
	1 x 10 ⁻²	2	Lemon juice
	1 x 10 ⁻³	3	Vinegar
	1 x 10 ⁻⁴	4	Soda
	1 x 10 ⁻⁵	5	Rainwater
Neutral	1 x 10 ⁻⁶	6	Milk
	1 x 10 ⁻⁷	7	Pure water
Bases	1 x 10 ⁻⁸	8	Egg whites
	1 x 10 ⁻⁹	9	Baking Soda
	1 x 10 ⁻¹⁰	10	Tums [®] antacid
	1 x 10 ⁻¹¹	11	Ammonia
	1 x 10 ⁻¹²	12	Mineral Lime - Ca(OH) ₂
	1 x 10 ⁻¹³	13	Drano [®]
	1 x 10 ⁻¹⁴	14	NaOH

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Review of osmolarity and pH

- Titratable acidity
 - increases the phlebitic potential
 - a measure of the reservoir of H⁺ ion in the solution
 - high titratable acidity irritates venous endothelial cells over a longer distance from the catheter tip
 - common to parenteral nutrition



What pH damages cells?

- pH's of 2.3 and 11 have been shown to kill cells on contact
- As the pH moderates, the cells survive for a longer time period
- Cell cultures at pH 4 survived for 10 minutes. Same for pH 9?
- pH is logarithmic, so pH 5 to 8 safer?



Mitigating factors

- Buffering systems
 - Stabilize the pH
 - The bicarbonate system keeps blood pH near 7.35
 - The time to neutralize the pH is a function of the strength of the acid or base and the titratable acidity



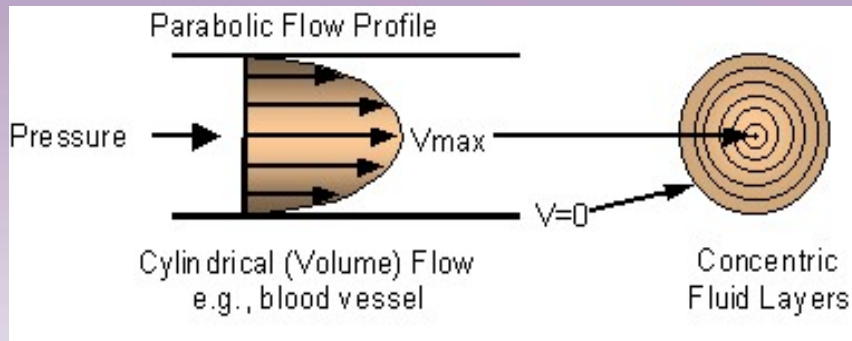
Mitigating factors

- Laminar flow

- laminar flow is a layer parallel to but separate from the surrounding blood flow
- slow diffusion of blood at the contact surface
- cells downstream exposed to the irritating solution.
- predominance of damage on the lower part of the venous lumen
- supports finding that faster infusion rates reduce phlebotic potential



Laminar Blood Flow



- Laminar flow is characterized by concentric layers of blood moving in parallel down the length of a blood vessel.
- The highest velocity is found in the center of the vessel.
- The lowest velocity is found along the vessel wall.



Cytotoxic drugs

- Certain infusates produce phlebitic changes despite being isotonic and pH neutral.
- Drugs can alter endothelial cell metabolism, cause cell-cycle arrest, inhibit DNA synthesis, and induce inflammatory responses

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Cytotoxic drugs

- Few trials have been conducted and even fewer drugs have been tested for direct cytotoxic effects on vascular endothelial cells
- With the exception of some chemotherapy drugs, toxicity is concentration dependent
- This validates the use of lower concentrations, slower infusion rates, and larger blood vessels.
- Macrolides (erythromycin, azithromycin)
- Quinolones (ciprofloxacin, levofloxacin)
- Penicillinase-resistant penicillins (nafcillin, oxacillin)
- Penems (imipenem, meropenem)
- Quinupristin/dalfopristin (Synercid®)
- Amphotericin B
- Vancomycin
- Foscarnet
- Antineoplastics (cladribine, mitomycin)
- Steroids (reversible)
- Cyclosporin (reversible)
- Pamidronate



Phlebitis in vivo

- Animal data isolates traumatic effect of pH and osmolality
 - Six hour infusions through peripheral vessels:
 - pH 4.5 = 100% severe phlebitic changes,
 - pH 5.9 = mild to moderate phlebitis in 50%,
 - pH 6.3 = mild damage in 20%, and
 - pH 6.5 = no significant damage



Phlebitis in vivo

- Animal data isolates traumatic effect of pH and osmolality
 - At pH 6.5, extending infusion duration produced no additional phlebitis
 - At pH 3 to 11, no phlebitic changes when given bolus
 - At pH 5, infused over 5 hours, 1 hour, or 30 minutes, phlebitis less with faster infusions



Phlebitis in vivo

- Animal data isolates traumatic effect of pH and osmolality
 - No studies of slowing infusions to reduce phlebitis
 - With peripheral parenteral nutrition, pH and titratable acidity cause phlebitis
 - The higher the titratable acidity, the greater the proximal and distal phlebitic changes

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Phlebitis in vivo

- Animal data isolates traumatic effect of pH and osmolality
 - Tolerance osmolarity of peripheral vessels in animals
 - 820 mOsm/kg for 8 hours,
 - 690 mOsm/kg for 12 hours, and
 - 550 mOsm/kg for 24 hours.
 - Faster infusion of hypertonic infusates resulted in greater vein tolerance



Phlebitis in humans

- The exact point at which osmolarity and pH become a liability in humans is unknown because of the variables involved in that determination
- There is significant interpatient variability in results of these trials



Phlebitis in humans

- The most cited human study of osmolality-induced phlebitis found:
 - the lowest risk of phlebitis occurred with solution osmolalities under 450 mOsm/L,
 - moderate risk at 450 to 600 mOsm/L and
 - highest risk over 600 mOsm/L
- Helped establish 600 mOsm/L as the outer limit of peripheral vein tolerance



Phlebitis in humans

- Human trials measuring the impact of pH on peripheral veins found:
 - neutralizing the pH to 7 - 7.4 significantly reduced the incidence of phlebitis
 - 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



Phlebitis in humans

- The INS pH 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

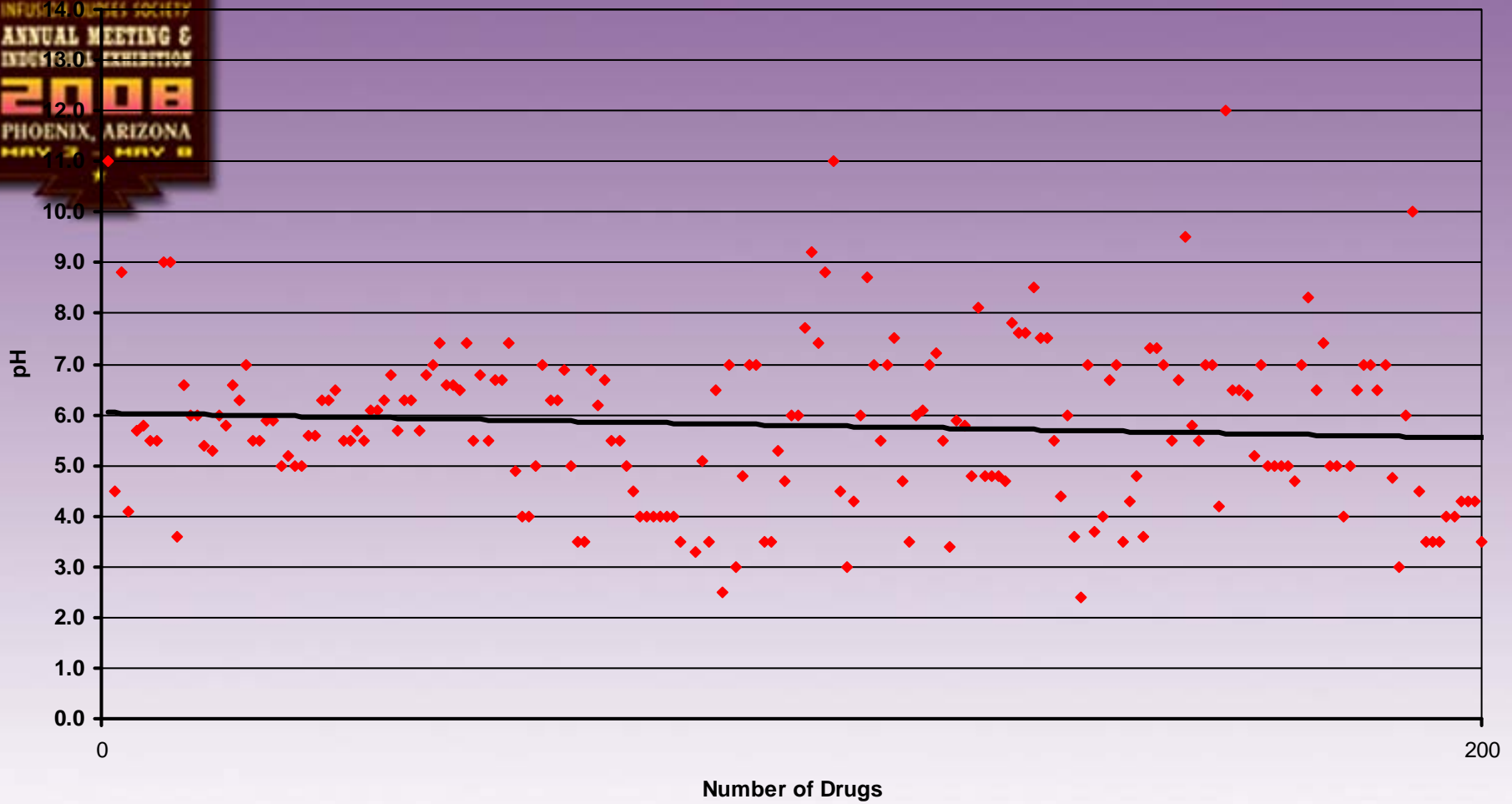


Measured pH and osmolality

- When plotted by pH and osmolality
 - Most drug solutions fall within the pH range of 5 to 9, but many are less than pH 6 and a significant number in the 3-5 range
 - Almost all drug solutions osmolalities are below 500 mOsmol/L



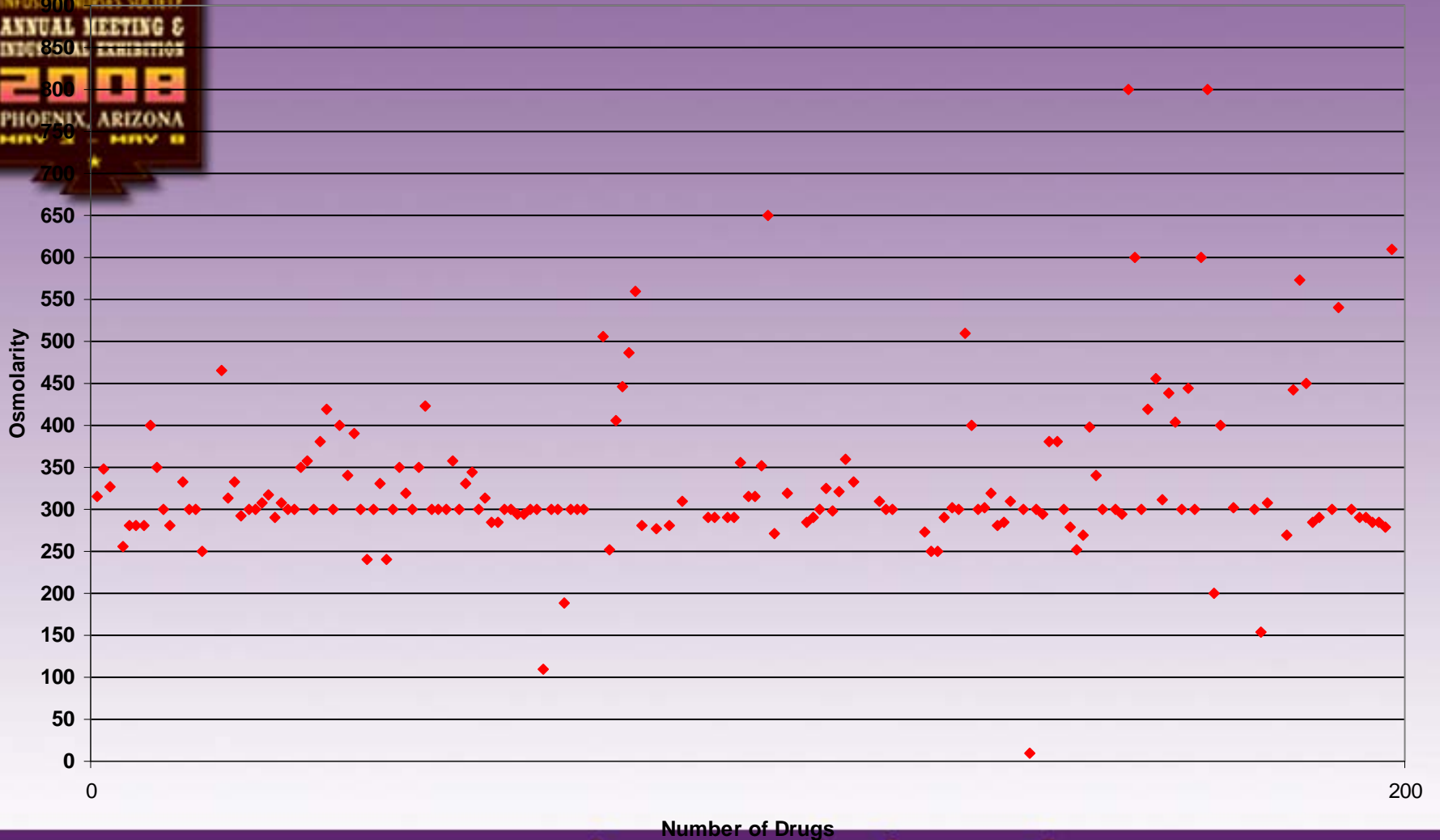
pH Distribution - Infusion Drugs



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Osmolarity Distribution - Infusion Drugs



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Modifying pH and osmolality

- Osmolality is not a primary cause of infusion phlebitis (without peripheral parenteral nutrition)
 - If the osmolality is > 400 , change the diluent to sterile water or $\frac{1}{2}$ NS
 - Ready-to-Use drugs are usually isotonic
 - Co-infusion of drugs with running hydration solutions will reduce the osmolality of the drug solution



Modifying pH and osmolality

- pH is a primary cause of infusion phlebitis
 - The drug pH profile determines the product formulation pH
 - This pH results in optimum stability or solubility
 - Optimum drug stability is usually found at the extremes of pH
 - Manufacturers get as close to pH 7.35 as the pharmaceutical parameters permit.



Modifying pH and osmolality

- pH is a primary cause of infusion phlebitis
 - Dextrose solutions are acidic because dextrose decomposition increases as the pH rises toward 7
 - Saline solutions are stable at a neutral pH, but are made acidic to enhance drug additive stability.



Modifying pH and osmolality

- pH is a primary cause of phlebitis
 - Parenteral nutrition solutions are acidic to enhance electrolyte solubility. Calcium phosphate precipitation increases as pH increases
 - Diluents can increase pH. A drug with a pH of 4.7 in NS has a pH of 4.9 in D5RL, a pH of 5.0 in D5Plasmalyte 56, and a pH of 5.5 in Sodium Lactate.



Summary

- Osmolality of drug solutions is not a primary concern when considering the overall causes of peripheral phlebitis
- pH is and will remain a significant cause of phlebitis in peripheral veins. One might call it **pHlebitis**



Summary

- INS standards suggest a range of pH 5 to 9 as peripherally tolerable.
 - Animal and human data suggest that a lesser variance from pH 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

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Summary

- Pharmacists are not necessarily aware of pH and osmolality data
- Pharmacists use charts, texts, and more often computer data to decide on dilution, stability, and infusion rates. The addition of pH and osmolality to these sources will assist in identifying candidates for central catheters