

New Perspectives on Vancomycin Use in Home Care, Part 1

Abstract

With the advent of new venous access devices (VADs) and medication delivery technology, pharmacists must reconsider the historical literature and administration guidelines that pertain to vancomycin. Current literature¹⁻³ supports the conclusion that there is no direct correlation between vancomycin concentration or rate of administration and side effects (particularly red man syndrome). Venous access devices such as midclavicular catheters, midlines, and peripheral inserted central catheters (PICCs) enable more concentrated solutions of vancomycin to be infused safely without an increased incidence of adverse events. Advances in medication delivery technology ensure the consistency of therapy protocols (including catheter flushing and administration rate) that reduce the potential for adverse events and medication errors, particularly in the unmonitored home setting.

The American Society of Health-System Pharmacists⁴ states that by fulfilling their responsibilities in pharmaceutical care, pharmacists have a role in meeting the primary care needs of patients. Pharmaceutical care is the direct, responsible provision of medication-related care to achieve an outcome that improves a patient's quality of life. Pharmacists establish relationships with patients to ensure the appropriateness of medication therapy, to verify patients' understanding of that therapy, and to monitor the effects of treatment. In collaborative drug therapy management, physicians and other prescribers authorize pharmacists to select appropriate medication therapies and regimens and adjust them on the basis of patients' responses to treatment.

The delivery of pharmaceutical care requires specialized knowledge about pharmacology, vascular access devices and their placement, compounding factors (eg, osmolarity, pH, stability, particulate matter), delivery systems, and patient management. In this article, those factors will be addressed with respect to optimizing the medication delivery of and patient response to vancomycin therapy.

Pharmacologic Characteristics of Vancomycin

Vancomycin is derived from the bacterium *Streptomyces orientalis*, which was isolated from the soil of India and Indonesia in 1956.⁵⁻⁷ Since 1958, it has been used to treat gram-positive bacterial infections (specifically those produced by staphylococci and enterococci). It is particularly effective against methicillin-resistant *Staphylococcus aureus* (MRSA), which is a prevalent nosocomial pathogen in the United States.⁸

The mechanism of action of vancomycin involves inhibiting bacterial cell wall synthesis. Unlike the aminoglycosides gentamicin and tobramycin, vancomycin has no significant postantibiotic

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effect, which is defined as the continued suppression of bacterial growth despite the decline of the antimicrobial concentration to zero.

Vascular Access Devices and Placement

Decisions about the dilution of vancomycin depend on the type of vascular access device used and its placement. When vancomycin was first approved for use in the late 1950s, the vascular technology available for the administration of any parenteral medication, especially irritating agents like vancomycin, was limited to over-the-needles catheters. The recommendations of Eli Lilly (the original manufacturer of vancomycin) for dilutions of vancomycin 5 mg/mL pertained to the available technology when the Food and Drug Administration (FDA) approved the drug. To this day, the dilution legacy of vancomycin 5 mg/mL fails to take into consideration the advances in vascular access technology. Unless there is a financial incentive to modify drug packaging (which includes dilution and the rate of administration), pharmaceutical companies do not change drug labeling to reflect the advances in vascular access devices and medication delivery or the practical experience gained by using a medication. Even though the use of a drug in clinical practice often differs from packaging recommendations, the cost of performing the necessary studies to justify labeling changes is not economically feasible for most pharmaceutical companies.

The vascular system can be accessed peripherally or centrally. In this article, central venous catheters (eg, Hickman, Broviac, or Groshong) are not addressed because they are used less frequently in the home infusion setting, especially in patients who receive only parenteral antibiotic therapy. Vascular access devices used peripherally are categorized as follows:

- Winged needle sets (“butterflies”)
- Over-the-needle peripheral (“Hep-lock”)
- Midline
- Midclavicular
- PICC

Each type of device type is defined in greater detail in Table 1. It is important to recognize that the use of the terms “midline,” “midclavicular,” and “PICC” have been historically fraught with inconsistencies in nomenclature, indications, care, and maintenance procedures. The importance of using established definitions of the

types of catheters consistently is critical because it enables consistency in clinical practice and a greater understanding of physiologic factors in the degree of blood dilution surrounding the catheter tip. That information is important when medication is administered. The Infusion Nurses Society, which was known as the Intravenous Nurses Society (INS),⁹ has developed position papers on and the following definitions of midline and midclavicular catheters and the PICC:

- Midline: A peripherally inserted catheter, the tip of which terminates in the proximal portion of the extremity¹⁰
- Midclavicular: A peripherally inserted catheter, the tip of which is positioned in the proximal axillary or subclavian vein¹⁰
- PICC: A peripherally inserted catheter, the tip of which is positioned in a central vessel (thoracic or superior vena cava); the position of the catheter is then confirmed via fluoroscopy or radiograph¹¹

Peripherally inserted catheters are categorized by their length, insertion site, and tip location. Table 1 illustrates the characteristics of each type of peripheral catheter.

Determining the location of the catheter tip is one of the greatest challenges of working with peripherally inserted catheters. This is especially true in home infusion patients whose catheter was inserted during a hospital stay. Obtaining a copy of the radiographic report confirming tip placement is ideal but is not always possible. Collaborating with members of the healthcare team (physicians, nurse clinicians, and others) who can obtain documentation on the insertion or placement of the vascular access device is important. A catheter insertion report that includes the length of the catheter can usually be provided by a licensed, certified (if required by state law or company policy) homecare clinician. That

report provides the critical information necessary to match the final parenteral product specification (dilution, diluent, rate of administration, and delivery system) with the catheter type.

Compounding Considerations for Vancomycin

Three characteristics of solutions and medications (solution osmolarity, pH,¹² and particulate matter) must be considered to determine the optimal dilution, rate of administration, stability, and delivery system for vancomycin.

Solution Osmolarity

Osmolarity is a calculated value for all chemical components of a solution, including the diluent. An appreciation of the concepts of osmosis and osmotic pressure is the key to understanding solution osmolarity. Osmosis is the diffusion of solutes (dissolved particles) or the transfer of fluid through semipermeable membranes such as blood vessels or cells. Osmotic pressure, which facilitates the transport of molecules across membranes, is expressed in osmolar concentrations and is referred to as hypo-osmotic (hypotonic), iso-osmotic (isotonic), or hyper-osmotic (hypertonic) when compared with biologic fluids such as blood. The term "tonicity" and "osmotic pressure" are often considered synonymous.

The osmolar concentration of parenteral solutions can exert adverse effects on the blood cells and vessels of the human body. Tonicity can be calculated for fluids and dissolved medications, which are expressed in a numerical value of milliosmoles per liter of fluid (mOsm/L). This value is also known as osmolarity.

The osmolarity of blood ranges between 285 and 310 mOsm/L. When hypotonic or hypertonic solutions are infused, fluid shifts

Table 1. Characteristics of Peripheral Catheters.

Characteristics	Winged Needle Sets	Over-the-Needle Peripheral	Midline	Midclavicular	PICC
Length	3/4 inches to 7/8 inches Referred to as butterfly catheter	Less than 3 inches in length	6 inches to 8 inches in length	Typically greater than 8 inches Placement of catheter tip determines definition	Typically greater than 8 inches and less than 21 inches Placement of catheter tip determines definition
Insertion site	Any available superficial vein	Superficial veins of the: <ul style="list-style-type: none"> • Scalp • Upper extremity • Lower extremity 	1 inches to 2 inches below or above the antecubital fossa: <ul style="list-style-type: none"> • Basilic • Cephalic 	1 inches to 2 inches below or above the antecubital fossa: <ul style="list-style-type: none"> • Basilic • Cephalic 	1 inches to 2 inches below or above the antecubital fossa: <ul style="list-style-type: none"> • Basilic • Cephalic
Tip location	Immediate vein	Immediate vein	Upper basilic or cephalic vein to the level of axilla Does not reach the axillary vein	Proximal axillary, subclavian, or brachiocephalic (innominate) vein	Thoracic or superior vena cava Requires radiographic confirmation

PICC = Peripheral inserted central catheter.

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into or out of cells, especially the endothelial cells of the inner layer of the peripheral blood vessels (tunica intima) near the catheter tip. This results in changes to the cell size of the vein wall, which in turn initiates inflammatory and clotting processes that cascade into phlebitis and thrombosis. The osmolarity of intravenously administered fluids dictates whether the solution should be delivered via the peripheral or central venous route because intravenous fluids interact directly with blood vessels and blood cells. The characteristics of solution tonicity are as follows:^{13,14}

Characteristics of Hypotonic Solutions

- They exhibit a tonicity of less than 240 mOsm/L.
- Examples include sterile water for injection and 0.45% sodium chloride injection.
- When hypotonic solutions are infused, a fluid shift occurs and water is moved into the endothelial cells of the vein and blood cells.
- Vein irritation, phlebitis, and hemolysis result when cells absorb too much water and burst.

A hypotonic solution should not be infused directly into a patient but can be used as a diluent for electrolytes or other medications.

Characteristics of Isotonic Solutions

- They exhibit a tonicity between 240 and 340 mOsm/L.
- Examples include 0.9% sodium chloride injection and 5% dextrose injection (D₅W).
- When an isotonic solution is infused, no fluids move in or out of cells.

Characteristics of Hypertonic Solutions

- They exhibit a tonicity greater than 340 mOsm/L.
- Examples include 10% dextrose injection and multiple-additive formulations such as parenteral nutrition.
- When a hypertonic solution is infused, water is drawn out of the vessel cells, which shrink. Chemical phlebitis, vessel irritation, and thrombosis may result.
- Solutions with an osmolarity greater than 600 mOsm/L should not be used peripherally (in over-the-needle or midline catheters).
- Usually, peripheral parenteral nutrition solutions exhibit an osmolarity between 600 to 900 mOsm/L. Solutions in excess of 900 mOsm/L that are administered peripherally into a small vessel with a conventional over-the-needle catheter often cause chemical phlebitis, vessel irritation, and thrombosis.

Calculating Osmolarity

The osmolarity of any pharmacy-prepared sterile product can be calculated by using the following formula:¹⁵

$$= \frac{\text{wt of substance (g/L)}}{\text{molecular weight (g)}} \times \text{number of species} \times 1000$$

The term “species” refers to the number of ions or chemical species formed when dissolution occurs. The following example can be used to calculate the osmolarity of vancomycin:

$$\begin{aligned} &= 1 \text{ g/100 mL} \times 1000 \text{ mL/L} \\ &= 10\text{g/L} \times 3 \text{ (number of species)} \times 1000 \\ &= 30,000/1468 \text{ (MW)} = 20.4 \text{ mOsm/L} + 0.9\% \text{ sodium} \\ &\quad \text{chloride injection (308 mOsm/L)} \\ &= 328 \text{ mOsm/L} \end{aligned}$$

The osmolarity of vancomycin 1 g in 100 mL of 0.9% sodium chloride injection is calculated to be 328 mOsm/L. This compounded vancomycin product is an isotonic solution relative to blood. As such, it does not produce an osmolar effect on biologic fluids and therefore should not contribute to an increased incidence of side effects when used with any type of vascular access device. Vancomycin 2 g in 100 mL of 0.9% sodium chloride injection has a calculated osmolarity of 348 mOsm/L.

This compounded vancomycin product is an isotonic solution relative to blood. As such, it does not have an osmolar effect on biologic fluids and thus does not contribute to an increased incidence of side effects when used with any type of vascular access device.

In a small study conducted in a laboratory at MD Anderson Cancer Center for this article, several significant differences were observed when the Lilly brand of vancomycin (Vancocin, Eli Lilly and Company, Indianapolis, Indiana) was reconstituted with sterile water to yield a final concentration of 50 mg/mL (LA Trissel, oral communication, June 2001). The osmolarity of that solution is 50 mOsm/kg via osmometer. In Table 2, the pH and osmolarity of vancomycin in final, “patient-ready” concentrations measured by laboratory instruments are shown. This actual measurement illustrates that using theoretic calculations may not be the most accurate method of determining solution osmolarity. It also illustrates that these solutions are hypotonic and thus must be infused into a blood vessel that provides the greatest amount of hemodilution.

pH

The pH of blood usually ranges between 7.35 and 7.45, which is considered neutral. Drugs with a pH value below 7 are considered acidic drugs, and those with a pH value below 4.1 are considered very acidic. Drugs with a pH value higher than 7.5 are considered basic or alkaline drugs, and those with a pH value higher than 9.0 are considered very alkaline. Very acidic or very alkaline drug-solution combinations can cause phlebitis and thrombosis. Buffering the drug minimizes its effect on pH. Most drug-solution combinations should not be pH buffered because of potential product

Table 2. The pH and Osmolarity of Vancomycin in Final, “Patient-ready” Concentrations.

Drug	Normal Saline	Dextrose 5% Water	pH
Vancomycin 1 g/100 mL	255 mOsm/kg	230 mOsm/kg	3.4 - 3.5
Vancomycin 2 g/100 mL	227 mOsm/kg	187 mOsm/kg	3.3 - 3.4

Table 3. Recommendations for Solution Osmolarity and pH To Minimize Phlebitis and Thrombosis.

Vessel	Catheter Type	Blood Flow (mL/min ⁹)	Osmolarity (mOsm/L)	Solution pH
Superior vena cava	CVC or PICC	2000	Greater than 900 mOsm/L	Less than 5 or greater than 9
Subclavian vein and/or proximal axillary vein	Midclavicular	800	Between 600 to 900 mOsm/L	Less than 5 or greater than 9
Cephalic and basilic veins in the upper arms	Over-the-needle catheter or midline	40 to 95	Less than 600 mOsm/Liter	Between 5 and 9

CVC = Central venous catheter PICC = Peripheral inserted central catheter

precipitation. Hemodilution is the best way of minimizing the vascular complications associated with hypotonic, hypertonic, very acidic, or very alkaline solutions.

Because of its pH, vancomycin is considered a vesicant (it has the potential to cause extravasation). Diluted vancomycin (5% aqueous solution), which has a pH of 2.4 to 4.5,¹⁶ should not be

administered intramuscularly because of the potential for tissue necrosis. Parenteral vancomycin should only be administered intravenously.

Diluted vancomycin in greater volumes of fluid (250 mL or more) does not increase pH significantly because the solutions themselves have no buffering capacity. The best method of addressing the pH of vancomycin is that of infusing the drug through a catheter with a tip location in a vessel that will allow for adequate hemodilution. If ideal venous access is not possible, routine rotation of the site and informing the patient of the signs and symptoms of phlebitis are important in preventing morbidity. In Table 3, the average blood flow and the recommended solution osmolarity and pH that must be infused to minimize phlebitis and thrombosis are featured.

In fluid-restricted patients with central venous access (which can include midclavicular and PICC lines), 1 g vancomycin can be diluted in as little as 60 mL of fluid.¹⁷ A study by Vickery et al³ indicated that 1 g vancomycin in 50 mL of fluid administered over 60 to 90 minutes via a midclavicular or peripherally inserted central venous access device is a safe, convenient, and efficient method of administration.

Stability

Vancomycin solutions diluted in the range of 5 mg/mL to 10 mg/mL are stable for extended periods of time and are ideal for homecare patients. The best sources of accurate information on stability are infusion device manufacturers who have conducted stability studies for drugs used in their equipment or a reference such as Trissel's *Handbook of Injectable Drugs*.¹⁸ A recent stability study of vancomycin 10 mg/mL in 0.9% sodium chloride injection in ethyl vinyl acetate (EVA) remained stable for 30 days at 4°C and for 7 days at 23°C (Tandem Medical Inc, unpublished data, January 2001).

Particulate Matter

Particulate matter is another factor that should be considered when the compounding of sterile drug products such as vancomycin is reviewed. Particulate matter, which usually consists of microscopic particles of undissolved drug that range in size from 5 to 20

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scopic particles of undissolved drug that range in size from 5 to 20 µg, can be found in drug solutions reconstituted from lyophilized powder. When infused, the particles can cause mechanical phlebitis to the tunica intima, and the use of a built-in or attached filter is recommended to minimize particulates. Using (at least) a 5-µg filter during the preparation of medications greatly reduces the amount of particulate matter of drug in solutions, which contributes positively to the patient's health and well-being.¹⁹

Rate of Administration

Historically, the rate of administration was thought to minimize the risk of red man's syndrome and other drug-related side effects. However, in a recent study²⁰ each of 16 critically ill patients who had undergone open-heart surgery received infusions of 1 g of vancomycin in 50 mL over 30 minutes. Only one of those patients developed red man's syndrome, but that patient experienced none of the adverse hemodynamic effects that can occur when vancomycin is infused rapidly.

When a catheter cannot be inserted into a large blood vessel that has a good hemodilution factor, slow infusions are of benefit. Slowly infusing vancomycin, which has a low pH, over 90 to 120 minutes allows blood vessels with lower hemodilution factors to diffuse smaller volumes of solution more effectively and thus prevents phlebitis. However, in large vessels with good hemodilution, the rate of administration appears to have no correlation with such side effects.

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