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Vancomycin

New Perspectives on an Old Drug

Abstract

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The use of vancomycin continues to be prevalent in all clinical settings. However, many questions persist about infusion techniques. According to the Infusion Nursing Standards of Practice, *peripheral catheters are not the best choice for infusing this drug because of its pH. The key to reducing risk of peripheral phlebitis and extravasation injury is choosing a more appropriate vascular access device. Many healthcare providers correlate systemic side effects with the infusion rate and concentration, although many reports cannot support this correlation. New technologies of vascular access and infusion controlling devices are changing old, established practices. This update provides an examination of the current literature on all aspects of infusing vancomycin and monitoring patients.*

Vancomycin was derived in 1956 from the bacterium *Streptomyces orientalis* found in soil of India and Indonesia.[1] This potent glycopeptide antibiotic kills gram-positive organisms, especially staphylococci and enterococci by hindering cell-wall synthesis.

During the last decade, several factors converged to increase the use of vancomycin. First, *Staphylococcus aureus* is a major cause of both community-acquired and nosocomial infections. In the United States, *S aureus* accounts for about 20% of all bacteremias. Additionally, several *S aureus* strains have become resistant to penicillin, semi-synthetic pencillins (eg, methi-

cillin, nafcillin and oxacillin), macrolides, tetracycline, and aminoglycosides. Because of growing concerns over methicillin-resistant *S aureus* (MRSA), coagulase-negative staphylococcus, and *Clostridium difficile*, vancomycin became the preferred therapy for staphylococcal infections, especially nosocomial infections.[2]

The incidence of vancomycin-resistant enterococci rose dramatically during the early 1990s.[3] Strains of *S aureus* with reduced susceptibility to vancomycin have been reported in the United States and Japan and it is labeled by the Centers for Disease Control and Prevention (CDC) as an emerging infectious disease threat.[4] In July 2002, the CDC released a report of the first case of *S aureus* fully resistant to vancomycin from a culture of the exit site and catheter tip of a temporary dialysis catheter.[5] Guidelines for prudent use of vancomycin have been established, including reducing its use and preventing the spread of organisms between patients. Alternative antibiotics include linezolid and quinupristin/dalfopristin. However, these drugs have additional risk and costs that are beyond the scope of this discussion.

The infusion of vancomycin continues to increase and present challenges. The infusion nurse must be aware of these challenges and prepared to collaborate with the physician and pharmacist to ensure positive patient outcomes from its use.

● COMPOUNDING CONSIDERATIONS

When vancomycin was introduced in the late 1950s, vascular access and infusion therapy was in its infancy, with few options for the type of catheter or drug delivery system. The original instructions for use from Eli Lilly, the first manufacturer, stated a dilution of 5 mg/mL. Common practices were catheters placed in peripheral veins. Subclavian insertion sites were described in 1952[6] and studies from 1957 through 1962 described reaching the central venous system through veins of the arm and legs.[7] A drug company must conduct clinical studies to support the change of any data contained in the package insert for any drug, including the dilution and rate of administration. Although clinical practice may vary, there usually is no financial incentive for manufacturers to conduct these studies to revise the instructions for use.[1]

The available options for central venous catheters today far exceed these limitations. Ambulatory infusion devices preferred for alternative care settings require small dilution volumes and greater concentrations. Concentrations of 10 mg to 20 mg of vancomycin per mL of diluent can be infused through a central venous catheter.[8]

Osmolarity

Osmolarity of the final admixture is an important characteristic that can affect vein irritation. An osmol is the unit of measure representing the number of solutes in a given solution. Osmolarity, expressed as mOsm/L, is a value calculated on the total number of osmols per liter of solution, while osmolality is the number of milliosmoles per kilogram of solvent.[9,10] Osmolarity, the term most commonly used, is calculated using the formula in Table 1. The molecular weight for each drug is found in the description section of the drug information. Species represents the number of ions formed when the drug is dissolved. Number 1 represents drugs that are not salts; number 2 represents drugs that are monovalent salts and electrolytes; number 3 represents drugs that are divalent salts and electrolytes.[11]

Tonicity is used interchangeably with osmolarity, particularly when applied to IV fluids. Hypotonic solu-

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TABLE 1

Calculating Osmolarity

Step 1. Calculate each ingredient in solution:

For vancomycin 1 gram in 100 mL NS, this calculation would be:

$$\frac{(g/mL \times 1000) \times (species \times 1000)}{Molecular\ weight\ of\ drug}$$

$$\frac{(0.01\ g/mL \times 1000) \times (3 \times 1000)}{1486} = 20\ mOsm/L$$

Step 2. Determine osmolarity of diluent

Sterile water = 0
Dextrose 5% in water (D5W) = 252
0.45% NaCl (1/2S) = 154
0.9% NaCl (NS) = 308

Step 3. Add all calculations   20 mOsm/L for vancomycin + 308 mOsm/L for normal saline = 328 mOsm/ L

tions have an osmolarity lower than body fluids, while hypertonic solutions have an osmolarity higher than body fluids. When hypotonic fluid is infused, osmosis occurs, causing water to move into the cells. Infusion of hypertonic fluids results in an osmotic shift of fluids out of the cells. This shift affects the endothelial lining of the vein wall, beginning the process of inflammation and thrombus formation.

Normal serum osmolarity is between 285 mOsm/L and 295 mOsm/L. Hypotonic solutions have an osmolarity less than 250 mOsm/L and hypertonic solutions are more than 375 mOsm/L.[12] The *Infusion Nursing Standards of Practice* recommends that solutions with an osmolarity greater than 500 mOsm/L are not appropriate for infusion through a short peripheral or midline catheter.[13] Changing the volume and type of diluent will alter the final osmolarity. The osmolarity of various vancomycin admixtures is described in Table 2, indicating that the calculated osmolarity of each admixture is an isotonic solution.

pH

Although admixture diluents and volumes can change osmolarity, they have little effect on final pH. Drugs are manufactured with the pH as close to physiological range as possible. Altering this pH during the admixture process could alter the stability of the drug, possibly causing precipitation. With a pH of less than 4.0 in most admixtures, vancomycin is classified as very acidic. The most appropriate way to address this problem is by infusing the drug into a central venous catheter. Blood flow in the superior vena cava around the catheter tip is approximately 2000 mL/min, providing rapid hemodilution to reduce vein irritation. The *Standards of Practice* also recommends that medications with a pH below 5 or above 9 are not appropriate

for infusion through a short peripheral or midline catheter.[13]

Stability

According to the *Handbook on Injectable Drugs*, vancomycin is stable after reconstitution for 14 days in refrigeration and room temperature.[14] Information from manufacturers of several types of elastomeric infusion devices indicates stability periods ranging from 24 hours to 17 days at room temperature.[11] Stability in an ethyl vinyl acetate (EVA) container was recently studied. An admixture of 10 mg/mL in 0.9% sodium chloride was stable for 30 days at 4°C and 7 days at 23°C.[1]

Particulate Matter

Vancomycin is a lyophilized powder requiring reconstitution. Particles of undissolved drugs ranging from 5µm to 20 µm in diameter have been found in reconstituted drugs.[1] Particles greater than 5µm in diameter can become lodged in capillaries of the lungs, which range from 7 µm to 12 µm in diameter.[15] The drug manufacturing process provides a high quality product. However, not all particles may have been eliminated. Filtration after admixture or during infusion will remove particulate matter.

Compatibility

Drug incompatibility is a physical or chemical phenomenon resulting in a concentration-dependent precipitation or a pH alteration. Solution changes include precipitation, haziness, or gas formation. Vancomycin is incompatible with numerous other medications. How-

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TABLE 2

Osmolarity and pH of Vancomycin Admixtures and Appropriateness of Vascular Access Device Use With Such Admixtures

Admixture	Calculated Osmolarity	pH*	Peripheral VAD	PICC
Serum/blood alone	285-295 mOsm/L	7.35-7.45	—	—
1g in 100 mL 0.9% sodium chloride	328	3.19	N	Y
1 g in 250 mL 0.9% sodium chloride	316	3.2 - 3.4	N	Y
1.5 g in 100 mL 0.9% sodium chloride	339	3.3 - 3.5	N	Y
1.5 g in 250 mL 0.9% sodium chloride	320	3.2 - 3.4	N	Y
2 g in 100 mL 0.9% sodium chloride	348	3.3 - 3.4	N	Y
2 g in 250 mL 0.9% sodium chloride	324	3.2 - 3.4	N	Y

VAD, vascular access device; PICC, peripherally inserted central catheter.
*pH values are subject to change over time. Clinical decisions about stability should be made based on the range of data points.

ever, heparin could produce the greatest concern. Physical incompatibility evidenced by a precipitate formation is seen when heparin and vancomycin are admixed in the same fluid container or syringe, and when one drug is injected through a Y-site of administration tubing containing the other drug.[14] The use of saline flushing before and after each dose of vancomycin is required to prevent contact with the heparin used in many catheter-flushing protocols. Adequate flushing may prevent accumulation of drug precipitate and reduce the risk of lumen occlusion. Aminophylline, amobarbital, aztreonam, chloramphenicol, dexamethasone, and sodium bicarbonate are incompatible with vancomycin when admixed in the same container. When given through a Y-injection site, it is incompatible with amphotericin B, aztreonam, numerous cephalosporins, foscarnet, nafcillin, piperacillin, propofol, ticarcillin, and several antineoplastic agents.

• INFUSION METHODS

Choices of Vascular Access Device

Vancomycin will cause tissue damage if it should escape from the vein into the subcutaneous tissue. Although common admixtures are isotonic, the acidic pH indicates the need for infusion through a central venous catheter. The length of therapy with vancomycin usually extends over many weeks. The chosen vascular access should allow for the delivery of the entire course of therapy with the minimal number of devices used.

Short peripheral or midline catheters should be avoided because of the potential for local phlebitis, thrombosis and tissue sloughing if extravasation occurs. Peripherally inserted central catheters (PICC) are the preferred choice for most infectious disease patients. However, a nontunneled percutaneous central catheter, tunneled catheter or implanted port may also be used.

Rate of Administration

Infusion rates for vancomycin have been studied extensively to correlate drug side effects with the infusion rate. These studies are usually in clinical settings such as operating rooms or intensive care units, where slow infusion is impractical. Rates as fast as one gram injected over 10 minutes have been studied. Early studies demonstrated an increased frequency of anaphylactoid reactions, while more recent studies with antihistamine pretreatment allowed this rapid infusion in 89% of patients studied.[16]

In a small study of 16 critically ill patients, infusion of one gram in 50 mL over 30 minutes did not produce changes in heart rate, blood pressure and several other cardiac indices. Following cardiopulmonary bypass surgery, hemodynamic data was collected from intra-arterial and pulmonary artery catheters before the vancomycin infusion. The same measurements were taken at 10, 20, and 30 minutes after the infusion, along with histamine and vancomycin plasma levels. All patients maintained stable heart rates, mean arterial pressure, central venous pressure, and several other cardiac measurements. In one patient, the histamine level increased significantly but returned to the baseline level 30 minutes after the infusion. This patient displayed signs of red-man syndrome (RMS) with a rash and itching of the chest and arms. However, this did resolve itself without treatment.[17]

Infusion of vancomycin during surgery is considered to be risky from the combined hypotensive effects of the anesthetic agents and vancomycin. Another study examined this issue through a randomized, double-blind study of patients undergoing elective orthopedic procedures. One group of patients received vancomycin 1g in 250 mL over 30 to 60 minutes prior to anesthesia induction, followed by 250 mL of normal saline. The second group of patients received the same solutions in reverse order: plain saline before anesthesia and vancomycin following anesthesia induction. They reported no hemodynamic changes in either group.[18]

Other studies have examined the concept of continuous IV infusion compared with the traditional intermittent infusion methods with mixed results.[19-22] Two studies found no improved activity of vancomycin and no change in the course of the disease process, concluding that continuous infusion was not worthwhile. The most recent of these studies found that microbiological and clinical outcomes between the randomized groups were similar. The authors concluded that continuous infusion may be more cost-effective than intermittent infusion. With continuous infusion, the total amount infused was less. However, this study did not include costs for volumetric infusion controlling devices, nurses' time and other disposable supplies.[23] This study also did not include an examination of the type of vascular access or the complex infusion therapies required for critical care patients.

Another approach compared one daily infusion with the conventional twice daily infusion, revealing the rates of side effects to be similar between the two groups of patients.[24] Although these recent studies may indicate future alterations, the most common rate of infusion is usually one hour. A central venous catheter to provide adequate hemodilution of the infusion is preferred. Although not recommended by the INS *Standards of Practice*, if peripheral veins must be used, choosing a small-gauge catheter (ie, 24 g), a large vein, and extending the infusion time over 1.5 to 2 hours may reduce vein irritation and localized phlebitis.

Delivery Methods

Options for infusing vancomycin include gravity flow controlled by roller clamps or other mechanical devices, volumetric infusion pumps, elastomeric balloon devices, and a multi-chambered fluid container placed in a portable infusion pump.

Flow control is an important consideration for the choice of infusion devices. Rapid infusion has been studied in controlled clinical situations with minimal negative outcomes, but flow control is needed to produce adequate serum concentrations.

Gravity infusions are usually regulated with a roller clamp and require frequent monitoring to ensure correct flow rate. Factors affecting their accuracy include the position of the catheter in relation to the vein wall or venous valve, patient movement, solution temperature, and height of the fluid container. Manual flow control devices can be added to the administration set. However, the accuracy rating of both the roller clamp and the add-on manual devices is plus or minus 10%.[25]

Although electronic volumetric infusion pumps are not easily adaptable for intermittent medications in the home care setting, they may be used in the hospital setting. Most electronic infusion pumps have an accuracy rating of 5% or less.[25] These devices also have the greatest range of programmable infusion volumes and rates.

Elastomeric balloon containers control flow rates by the size of the opening in the tubing at the point of attachment to the container. Once the clamp is opened, the collapsing balloon delivers the medication at a predetermined rate. Depending on the size of the container, the amount injected into the balloon, and the size of the opening, infusion rates range from 30 minutes to several days. They are used for intermittent doses of antibiotics and other drugs, including regional analgesia. Balloon sizes can accommodate volumes of up to 250 mL. The entire unit is disposable. The patient must be taught how to flush the catheter before and after the medication infusion.

Recently, a new type of portable infusion device was introduced for use with antibiotic therapy (AutoDose® Infusion System, Tandem Medical, San Diego). The system consists of a multi-chambered fluid container, or bag, designed to hold the pre-infusion saline, the drug and diluent, the post-infusion saline, and the heparin flush solution. The filled container is placed into the infusion device, which is powered by a mechanical roller. Opening the doors charges the device by uncoiling the roller. When the fluid container is loaded, the doors are closed, the system is started, and pressure is generated by the roller, forcing fluid out of each chamber in the correct sequence. The rate, which is controlled by restrictive tubing in the administration set that includes a particulate and air eliminating filter, can be chosen to flow at 200mL/h, 100mL/h or 67mL/h (allowing a 100 mL volume to infuse over 1.5 hours). This system allows the user to accomplish the entire SASH (Saline, Administer drug, Saline, Heparin) protocol with one connection to the catheter hub, ensuring proper flushing.

A large home care pharmacy recently reported a net savings of $5.74 per dose of antibiotic when using the AutoDose system. The standard method used had been gravity infusion with pre-filled syringes supplied for flushing. The costs of this method were compared with the costs of the AutoDose technique. A documented reduction of training visits for the AutoDose system also yielded a cost savings. Based on 18,000 doses annually, a total savings of $103,320, or a cost reduction of 23% compared with other infusion methods, was projected.[26]

● PATIENT MANAGEMENT

Dosing

Adult dosage is 15 mg/kg of body weight, rounded to the nearest 250 mg increment. The frequency of each dose is determined by the calculated creatinine clearance (CrCl), or the amount of fluid the kidneys are capable of filtering per minute. Dosing intervals every 12 hours requires CrCl of 70 mL/min or greater. As the CrCl decreases, dosing intervals increase to every 24, 48, or 72 hours.[8]

Pediatric doses are 10 mg/kg per dose infused every 6 hours. The neonatal dose is 15 mg/kg as an initial dose, followed by 10 mg/kg per dose every 12 hours for the first week after birth. From 1 week to 1 month of age, the dosing interval is usually every eight hours.[8]

Serum Monitoring

Much controversy exists over the issue of routine monitoring of serum levels of vancomycin. There is a lack of scientific evidence supporting the need for obtaining peak serum concentrations. No well-controlled studies have examined the cure rate in comparison with specific serum concentrations. Peak serum levels are dependent on accurate infusion flow rates and proper timing of the blood sample. Without adequate flow control, part of the dose may be eliminated from the body before the entire dose has infused. Timing the home visit for obtaining the blood sample following dose infusion can also be a challenge. For these reasons many are recommending reliance on trough levels only. Most organisms susceptible to vancomycin will be killed when the serum trough level is between five and 15 mg/L.[27] If trough levels exceed this amount, adjusting dosage intervals is preferred to decreasing the volume of the dose. In addition to the clinical benefit, costs are reduced because admixed

doses do not have to be wasted, just given at a later time. In home care, this will reduce delivery costs as well.

• ADVERSE DRUG REACTIONS

Renal, auditory, and central nervous system toxicity can occur with vancomycin. Monitoring for toxicity involves knowing the patient's additional risk factors such as medical history and all drugs the patient is receiving. Patient education provides another strategy to monitor outcomes. The patient should be provided with written information about signs and symptoms of toxicity and the actions to take. This information should use language appropriate for the patient's age and learning level. It is also helpful to make signs and symptoms relevant to everyday life. Examples include family complaints about having the television or radio too loud, indicating hearing loss or the exact color and amount of urine.

Renal toxicity is reported to be less than 5% when only vancomycin is being given. When combined with aminoglycosides, the incidence ranges between 8% and 35%.[27] The patient should be assessed for decreased frequency of urination, a darkening color of urine, peripheral edema, increased thirst, and dry skin.

Ototoxicity is usually seen in the form of tinnitus and loss of high-tone sounds, although this appears to be associated with high serum concentrations, usually above 80 mg/L.[27]

Central nervous system problems may be seen as headache, complaints of feeling lightheaded or dizzy, nausea, vomiting, or an unsteady gait.

Hypersensivity and RMS are actually two separate side effects, both related to the immune system and mast cells. Mast cells contain granules that house histamine and heparin. They are located in subcutaneous tissue, lungs, and the gastrointestinal tract. When stimulated, mast cells release their granules into the bloodstream. Other mediators such as prostaglandins and leukotrienes are created by lipid synthesis on the mast cell wall. Stimulation of mast cells occurs by four different mechanisms: immunoglobulin E (IgE), activation of complement proteins, physical and chemical.[28]

An allergic reaction, or hypersensitivity, is caused by the presence of IgE. The body has been exposed to the foreign antigen at some point in the past and has created a corresponding antibody. With subsequent exposure, an allergic reaction occurs. The severe form, an anaphylactic reaction, can be life threatening.

Complement proteins are found in the bloodstream and can stimulate mast cells. Physical stimulation comes from pressure, heat, cold, or vibration. Chemical stimulation occurs from the presence of drugs such as narcotics, angiotensin-converting enzyme inhibitors,

beta-blockers, and vancomycin. When these reactions are severe, they are known as anaphylactoid reactions; this syndrome is also known as RMS when associated with vancomycin infusion.

Regardless of the mechanism that causes the stimulation of mast cells, the clinical signs and symptoms are the same: skin flushing; erythematous rash on the face, neck and chest; itching; and hypotension. Although treatment is also the same, it is important to distinguish an IgE-mediated allergic reaction from a chemically induced RMS, as this knowledge will impact future healthcare. One study found that tryptase, another chemical released when mast cells degranulate, is present during an IgE-mediated allergic reaction, but is absent during a chemically induced RMS. Therefore, measuring plasma tryptase levels can assist with appropriate diagnosis.[29]

Many studies have tried to establish a link between the rate of vancomycin infusion and the incidence of adverse reactions, especially RMS. However, these reactions have been documented with all infusion rates, and at both high and low concentrations. RMS will usually occur with the first dose, but no apparent correlation exists between infusion rate or concentration of vancomycin and incidence or severity of RMS. The discomfort is managed by premedication with antihistamine, especially H1 and H2 antagonists.

• CONCLUSION

Clinical practice has changed tremendously since the original vancomycin instructions for use were written. Scientific evidence continues to expand our knowledge of patient outcomes, and it is clear vancomycin can be safely infused in a variety of healthcare settings.

A common nursing intervention to reduce venous irritation is to increase the volume of dilution. This strategy will not reduce vein irritation from vancomycin because there is little change in the pH and osmolarity of the final admixture. Infusion through a centrally placed catheter such as a PICC is recommended because there will be rapid hemodilution and less ensuing vein irritation. Side effects such as RMS appear to be an idiosyncratic event, unrelated to the rate of infusion or concentration of the drug.

Safe and effective administration of vancomycin is dependent upon appropriate collaboration between the physician, nurse and pharmacist. The type of vascular access device and infusion controlling device will impact decisions such as amount of dilution and rate of administration. Communication between these disciplines will lead to cost-effective and therapeutically appropriate choices, thus decreasing side effects and improving patient outcomes.

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