Use of Vancomycin in Pediatrics

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Vancomycin is a glycopeptide antibiotic, which acts on the bacterial cell wall. It was first used clinically in 1958.1 It is not well absorbed orally and is 80% to 90% excreted by the kidney.2 It’s absorption into tissues is variable and often poor, in part related to its relatively large size. Although it is a bactericidal antibiotic, it is generally less efficacious and bactericidal for a given organism than a corresponding beta-lactam to which the organism is susceptible.3 Its primary clinical utility thus lies in the treatment of infections with Gram positive organisms resistant to beta-lactam antibiotics (eg, methicillin-resistant Staphylococcus aureus (MRSA), coagulase-negative Staphylococci, penicillin-resistant Streptococcus pneumoniae central nervous system infections, etc.).

TOXICITY

Although frequently associated with nephrotoxicity, this finding has never been documented in animal models, and its descriptions in the literature are often confounded by concurrent administration of nephrotoxic drugs or systemic illness.2,4 In addition, most studies are small, retrospective and use varying definitions of nephrotoxicity. Early reports of nephrotoxicity may also have been in part related to impurities present in early preparations of the drug.2 Overall, nephrotoxicity in adult patients is estimated to be <5%.4–6 In addition, renal insufficiency induced by vancomycin is typically transient and resolves with removal of the drug.4,5 However, there are reports of an increased risk of nephrotoxicity when vancomycin is combined with an aminoglycoside, above and beyond any expected additive effects from the use of both agents together.2,6–8 Reports in the literature have estimated that vancomycin may increase the risk of nephrotoxicity in a patient with concurrent aminoglycoside use by 3- to 4-fold.5–7 Attempts to correlate specific vancomycin levels to a risk of developing nephrotoxicity have been inconclusive, although recent retrospective data have suggested a link to high trough levels.2,4,9,10 Although initially reported to be associated with ototoxicity, this association has been called into question. Many initial reports of ototoxicity occurred in patients with potential confounding factors (eg, concurrent meningitis and aminoglycoside use).9 Reports of potential vancomycin related ototoxicity are rare, and the exact relationship (if any) between levels of the drug and hearing loss are unknown.4,7,11–13 An association of erythema and flushing of the face, neck, and torso (Red Man’s Syndrome) occurs in a significant number of patients (up to 50% in some series) and is believed to be secondary to histamine release.11–13 It is most often described when doses are administered at a relatively rapid pace (over 1 hour or less).13 Vancomycin levels have not been correlated with a risk of developing the syndrome or with histamine levels.13 Decreasing the infusion rate to administer the drug over 2 hours has been correlated with lower levels of histamine release and improvement of clinical signs and symptoms.15 Administration of diphenhydramine before vancomycin infusion has been reported to mitigate this phenomenon as well.14

MONITORING

The optimal manner in which to monitor vancomycin levels is unclear. Two primary pharmacokinetic parameters exist for evaluation: the peak and the trough. Peak values for vancomycin are difficult to measure because extensive interpatient variability exists with regard to when a peak concentration is achieved in a given patient, and vancomycin has been demonstrated to kill in a concentration-independent fashion.5,11,16,17 Trough levels are technically easier to perform and are best performed after a steady-state has been achieved (~30 minutes before the 5th dose).5,11 The area under the curve (AUC) divided by the minimal inhibitory concentration (MIC) of the organism (AUC/MIC) has been reported to correlate with clinical outcomes better than trough levels in some clinical scenarios. Adult patients prospectively evaluated with Staphylococcal pneumonia and vancomycin AUC/MIC values >400 were reported to have significantly better outcomes (clinician report of resolution of disease) and bacteriologic responses (sterilization of cultures) than those patients with an AUC/MIC <400.18 In one retrospective study, adult patients with a Staphylococcal pneumonia and an AUC/MIC >345 had

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significantly better performance on a clinical scoring system than patients with an AUC/MIC <3.45. However intuitive and promising such a measurement may be, the calculation (AUC/MIC) is somewhat labor intensive and has not been validated in children. In addition, it has not been validated in infections other than pneumonia. In general, consideration should be given to monitor levels for all patients with preexisting renal insufficiency or a concern of potential renal insufficiency, those patients who are receiving concurrent nephrotoxic agents (especially aminoglycosides), or who will be on therapy with vancomycin for a prolonged period of time (eg, >10 days). In addition, some evidence suggests that the clearance of vancomycin may decrease after 10 days, arguing for a repeat level at that point in therapy whether the antibiotic is to be continued.29 Goal trough levels of 15 to 20 μg/mL may be required for regions of the body in which penetration may be a concern (eg, central nervous system and bone). In adult studies, this level corresponds to an AUC/MIC of ≥400, provided that the MIC for the organism is ≤1 μg/mL.5,18 More pediatric research into this issue is required. For regions of the body where either the infection is less severe or penetration is less of concern (eg, skin and soft tissue infections [SSTI]), lower trough levels may be acceptable.

DOISING

Commonly used vancomycin doses outside of the neonatal period range from 40 to 60 mg/kg/d divided every 6 to 8 hours.21,22 The exact dose will depend on the clinical presentation and may need to be altered based on the results of therapeutic monitoring.

VANCYMYCIN RESISTANCE

Resistance to vancomycin is increasing for many organisms, and this resistance has in turn been linked to poor clinical outcomes.23–25 In 2006, the Clinical Laboratory Standards Institute moved the “break point” for susceptibility of MRSA to vancomycin from ≤4 to ≤2 μg/L.5 However, many recent reports have documented poor clinical outcomes in patients infected with MRSA strains exhibiting MICs from 1.0 to 2.0 μg/mL.5,23–25 It should be noted that an AUC/MIC >400 is not attainable if an MRSA isolate has an MIC ≥1.5. Similar reports have been published involving S. epidermidis strains with MIC’s to vancomycin ≥2.0 μg/L.16 Hence, attention must be paid to the MIC of the organism and the clinical response of the patient whenever vancomycin is used. Should the MIC be on the higher end of the spectrum (eg, 1.0–2.0 μg/L for MRSA), one may need to consider an alternative agent, especially if the patient is not clinically improving. Some evidence suggests that keeping vancomycin trough levels >10 μg/mL may help prevent the development of heteroresistance in MRSA.26

COMMON CLINICAL SCENARIOS

Bone and Joint Infections

Vancomycin is most often used in this setting for the treatment of MRSA pyogenic arthritis and osteomyelitis. Penetration of vancomycin into bone is likely to be suboptimal and is not well studied.27 As a result, higher doses and levels may need to be used in an attempt to maximize bone and joint penetration.

Central Nervous System (CNS) Infections

Vancomycin may be needed for coverage of Gram positive infections of the CNS. This often occurs in neurosurgical patients, such as those with ventricular shunts, or those patients recently removed from craniofacial surgery, and in patients with brain abscesses requiring coverage of Gram positive flora. Penicillin resistant S. pneumoniae meningitis may also require the use of vancomycin.28 Penetration of vancomycin across the blood brain barrier is somewhat limited. As a result, higher doses and levels may be needed to maximize penetration. A dose of 60 mg/kg/d divided every 6 hours has been documented to produce a vancomycin CSF and serum concentration ratio of 0.21 in previously healthy children with acute bacterial meningitis.29 In exceptional circumstances, the use of a continuous vancomycin drip may be considered.

Bacteremia

MRSA may be a cause of bacteremia in immunocompetent hosts without indwelling central venous lines. Other Gram positive flora (eg, some Gram positive rods and coagulase-negative Staphylococci) are frequent causes of central venous line infections, which may require vancomycin therapy. High doses and levels of vancomycin may be needed, at least initially, given the potential severity of MRSA bacteremia and the propensity of S. aureus to disseminate to regions of the body in which vancomycin penetration may be variable. In addition, given the high prevalence of immunosuppression in many patients requiring prolonged central venous access, other common Gram positive infections of central venous catheters may likewise initially require high dosages and levels. For patients who have not obtained the desired trough level but are clinically improving with documented clearance of bacteremia, consideration should be given to leaving the patient on the current dose of vancomycin. In such an instance, the directly observed clinical improvement in the patient, taken in conjunction with the lack of correlation between specific vancomycin levels and clinical outcome in the literature, would argue for maintenance of the current dose.

Skin and Soft Tissue Infections (SSTI)

Skin abscesses, cellulitis, myositis, and fasciitis are frequently caused by MRSA, and may necessitate vancomycin coverage, at least until clinical improvement (and potentially surgical intervention) has occurred. Initial dosing and goal levels may vary greatly depending on the severity of the SSTI (eg, necrotizing fasciitis vs. a drained gluteal abscess), the presence of concurrent bacteremia, the age of the child, the immune status of the host, and the potential for surgical intervention. For uncomplicated SSTIs in immunocompetent hosts, lower doses of vancomycin divided for every 8 hours may be considered, depending on the aforementioned factors. For patients with a SSTI who are older than a year of age, with no preexisting renal insufficiency, a normal creatinine, a low suspicion of bacteremia and invasive disease, no concern of future renal insufficiency (eg, sepsis with secondary renal failure), and no use of concurrent nephrotoxic drugs (eg, gentamicin), consideration can be given to not assessing vancomycin trough levels. In such instances, a directly observed clinical improvement seen in the patient, taken in conjunction with the lack of correlation between specific vancomycin levels and clinical outcome in the literature, would argue for dosing not guided by drug levels. Patients not meeting the above criteria should have trough levels assessed. If a trough level is assessed and found not to be therapeutic, but the patient is clinically improving, consideration may be given to maintaining the current dose of vancomycin.

Pulmonary Infections

MRSA may cause pneumonia (either community acquired or nosocomial and ventilator associated). High doses of vancomycin and higher levels may be needed, given the potential severity of MRSA pneumonia and the poor and variable penetration of vancomycin into lung tissues2,29 and depending on the severity of the infection and the immunologic status of the host, empiric coverage with vancomycin may be desired until culture results are more mature. Consideration should be given to higher doses and levels of vancomycin at least until serious infection (eg, bacteremia and meningitis) can be excluded. Dosing frequency should be based on the level of concern of CNS

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involvement (q 6 hours vs. q 8 hours). Consideration should be given to monitoring vancomycin levels based on the suspected site of infection as discussed earlier.

Neonatal Dosing

Dosing of vancomycin in neonates is controversial. The volume of distribution in neonates is increased and the clearance decreased, leading to the potential for an increased half-life for the drug. Outside of the first week of life, some authors have suggested that alterations in vancomycin pharmacokinetics may have more to do with changes in body weight than gestational or postnatal age (although changes are commonly reported to correlate with these latter 2 parameters, these relationships may be confounded by body weight). Dosing guidelines vary widely depending on the source and institution.

SUMMARY

Vancomycin has been a useful antibiotic for ~50 years. The recent advent of MRSA and other antibiotic resistance to beta-lactam antibiotics has provided a renascence for this glycopeptide. However, much remains unknown about the pharmacology and safety for pediatric patients, particularly in neonates.

REFERENCES