1988-05

University Hospital Pharmacy Update: May 1988 v. 3, no. 3

Boston University Medical Center
The University Hospital, Department of Pharmacy at Boston University Medical Center

http://hdl.handle.net/2144/22576
Boston University
Effective May 2, 1988 with the opening of the new Atrium Pavilion Operating Room Complex, the Department of Pharmacy began to provide service to the OR via a satellite located in the clean area next to the neurosurgical suite. One technician will be on duty from 8:00AM to 4:30 PM on Mondays and 6:30AM to 4:30PM Tuesday through Friday to primarily assist in the distribution and record keeping of narcotics used in the OR by anesthesiologists. A pharmacist from the main pharmacy will periodically check the technician's work. All anesthesiologists will be required to obtain their narcotic supplies from the satellite prior to each case. On weekends and at night, the narcotics will be obtained from the main pharmacy on the second floor. The OR satellite will also be responsible for maintaining drug supplies in the Recovery Room, CT Supply Area and Holding Unit. Expansion of services to include a full-time pharmacist, preparation of IV admixtures, dispensing and distribution of all medications to the OR and Recovery Room is being planned.

New Standard TPN Available for After Hours

As a standard policy, all orders for TPN's must be received in the Pharmacy by 1PM. Except in unusual cases where workload permits, the Department of Pharmacy will not admix TPN's if the order is received in the Pharmacy after 1PM. This is due to the long time needed for compounding the TPNs and to assure that TPNs for all patients will be ready by the 5-6PM hang time. Since trained personnel are not available in the Pharmacy to make TPN's after 5PM, previously the only recourse for late orders was to hang a bag of D10W or wait until the following day. Now, a special standard formula is being made available for use in such cases.

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Drug Review: Vancomycin

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Reviewed By: Alan Sugar, M.D., Section on Infectious Diseases, Department of Medicine, The University Hospital

Although not a new drug, vancomycin has over the last 2 years become one of the most commonly used antibiotics in today's hospital practice. In many institutions (including UH), it has risen to become the number one drug in terms of dollars spent. The recent emergence of oxacillin resistant Staphylococci has fostered this rise. However, the dosing of vancomycin is much more complicated than most people believe and is more akin to aminoglycosides with dosage reductions required in renal failure than is natcillin/oxacillin, the drugs it usually replaces. Failure to reduce the dose in patient with even slight renal impairment can result in nephrotoxicity particularly if given in conjunction with aminoglycosides. Vancomycin serum levels should be monitored routinely as well as renal function tests when using this drug. The purpose of this discussion is to provide some insight into the complexities of dosing vancomycin and to present some of the currently recommended dosing methods, particularly for patients with renal impairment.

SERUM CONCENTRATION/ACTIVITY

Vancomycin is active only against gram-positive bacteria at clinical achievable concentrations. In vitro, at concentrations of 0.5 to 5 mcg/mL, it is active against many strains of streptococci including S. pyogenes, S. pneumoniae, staphylococci, Clostridium difficile, Clostridium perfringens, Corynebacterium, Listeria monocytogenes, Bacillus anthracis, actinomycetes, lactobacilli, diphtheroids, and Neisseria gonorrhoeae. However, levels as high as 10 to 20 mcg/mL may be required for some strains of Staphylococcus aureus. It is only bacteriostatic against enterococci. The recommended serum levels of vancomycin are a peak (post dose) level of 20-40 mcg/mL and a trough (pre-dose) level of 5-10 mcg/mL, which is significantly above the concentration needed again most gram positive organisms.

Vancomycin is indicated primarily in gram positive infections resistant to natcillin or in patients allergic to penicillin. If cultures/sensitivities from microbiology laboratory are reported as Staphylococcus sensitive to natcillin and the patient does not have a penicillin allergy, there is seldom reason to use the more expensive vancomycin. Natcillin/oxacillin has less dose related side effects and toxicities and is considerably less expensive.

PHARMACOKINETICS

Vancomycin's prolonged distribution phase occurs in three phases, and adds a degree of complexity to its pharmacokinetic profile. Vancomycin is primarily excreted by the kidneys with 80-90% of the dose unchanged in the urine. In patients with renal impairment, the elimination half-life of this drug is significantly prolonged. The half life of vancomycin varies greatly in anephric patients, ranging from 1.4 to 231 hours. This is significantly different from natcillin which is primarily metabolized by the liver. Natcillin dosing needs not be adjusted in renal failure as does vancomycin.

Vancomycin distributes to a volume that approximates total body water. Serum protein binding is moderate ranging from 44% to 82% (mean=55%). A larger volume of distribution of vancomycin was found in elderly patients, indicating a need for a higher dose to achieve therapeutic levels. This is considered to be caused by enhanced tissue binding of the drug in the elderly. This is combined with generally poorer elimination of vancomycin by the kidneys in the elderly suggests that elderly patients should be dosed with a high dose & longer dosing interval than younger patients.

Vancomycin does not penetrate well into the cerebrospinal fluid even with inflamed meninges and may require higher doses. Although controversial, the intrathecal administration of vancomycin has been used in treating meningitis, using a dose of 10-20mg every 24 hours.

A fall in serum concentration of vancomycin occurs after the initiation of cardiopulmonary bypass surgery, so a preoperative dose of at least 15 mg/kg is recommended to maintain adequate serum concentrations throughout out the cardiac surgery when vancomycin is used for prophylaxis. It should be noted that vancomycin's use in prophylaxis is extremely limited and should not be routinely considered as a prophylactic agent.

The dosage of vancomycin should be based on a total body weight instead of lean body weight in obese patients. In an uncontrolled study of six morbidly obese patients, a strong correlation between vancomycin clearance and total body weight was observed.
Drug Review: Vancomycin
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ADVERSE EFFECTS RELATED TO TOXICITY

The red neck syndrome (flushing, hypotension, erythema, and rash over the neck and upper torso) is a unique adverse reaction and perhaps the most common side effect related to vancomycin. It is related to a rapid infusion rate (greater than 500 mg over 30 minutes) and not to the dosage regimen of the drug, as some people erroneously believe. Such reactions can be minimized by increasing the dilution volume and by slowing the infusion rate to greater than 1 hour. Changes in the dosage regimen are not needed.

The most important side effect related to dosing toxicity with vancomycin is nephrotoxicity. The incidence of this side effect has not changed during the last 30 years, and hence are not related to the purity of the product. Nephrotoxicity is believed to be related to trough (pre-dose) serum concentrations over 30 mcg/ml. In a retrospective study of vancomycin toxicity in 98 patients, the incidence of nephrotoxicity was reported to be 5% when vancomycin is used alone. A significantly higher incidence (30-40%) of nephrotoxicity (rise in serum creatinine > 0.5 mcg/ml over baseline) was observed when vancomycin was used in combination with aminoglycosides. This effect was reversible following the cessation of vancomycin therapy. Serum creatinine levels should be monitored carefully (e.g. twice weekly) when vancomycin is given in combination with an aminoglycoside.

DOsing GUIDELINES

Since most of the associated toxicities of vancomycin are related to appropriate serum concentrations, much research has gone into determining the most appropriate dosing regimen for patients, especially those prone to toxicity - those with renal impairment. Table 1 summarizes currently accepted dosing guidelines published in the literature for initial vancomycin dosing.

<table>
<thead>
<tr>
<th>Table 1: Initial Recommended Dose</th>
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<tbody>
<tr>
<td>Normal Renal Function: 1gm q12h or 500 mg q6h (both regimens are equally effective, however, the 12 hour dosing interval is preferred because it is less costly)</td>
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<tr>
<td>Morbidly Obese Patients: 8mg/kg total weight q6h (&gt;2x lean body weight*)</td>
</tr>
<tr>
<td>Patients with Renal Dysfunction: 15mg/kg lean body</td>
</tr>
</tbody>
</table>

(estimated CrCl <75 ml/min) weight

CrCl=70-89 mL/min q18h
CrCl=46-69 mL/min q24h
CrCl=30-45 mL/min q36h
CrCl=15-29 mL/min q48h

Doses should be rounded to one of the following: 500 mg, 750 mg or 1g.

Lean body weight*= 50kg±2.3kg for every inch over 60 in (male) 45kg±2.3kg for every inch over 60 in (female)

CrCl (males)=(140-age in yrs) x Lean body weight (Serum Creatinine x 72)
CrCl (females)=CrCl (males) x 0.85

When desired serum peak and trough levels are not within the desired range, physicians are welcome to call the Department of Pharmacy for an in-depth pharmacokinetic analysis with resulting recommendation for dosing. As little as one pre-dose and one post-dose serum vancomycin concentrations drawn at the proper times can be used to derive patient-specific pharmacokinetic parameters (i.e. half-life, volume of distribution, etc.) which, in turn, are used to yield more accurate and patient-specific dosing recommendations. This method using standard pharmacokinetic equations derived for intermittent infusions is superior to both nomograms in terms of precision and has been used successfully at other institutions. The service is available at no cost, with a turnaround time of 2 hours or less. For information, contact the Drug Information Service at Ext. 6797.

THERAPEUTIC MONITORING

Monitoring vancomycin serum levels is important in maintaining the quality of patient care. Generally, serum samples should be obtained at steady state so the desired dose can be assessed by the levels. In patients with normal renal function, 24 hours usually is required for steady state to be reached. Table 2 summarizes the therapeutic range of peak and trough serum levels and when to draw the levels. In general, serum drug levels for vancomycin should be obtained after third dose.

<table>
<thead>
<tr>
<th>Table 2: Serum Levels</th>
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<tr>
<td>Therapeutic Serum Drug Levels: Peak: 20-40 mcg/ml Trough: 5-10 mcg/ml</td>
</tr>
<tr>
<td>Time of Levels: Peak: at least 1-3 hrs after end of infusion. Trough: just prior to next dose</td>
</tr>
</tbody>
</table>

In summary, maintaining therapeutic and avoiding toxic serum concentrations is an important consideration when dosing vancomycin. Prevention of unwanted toxicity and unnecessary cost is important to quality patient care. The dosing guidelines presented here, offer the practitioner a method of appropriately dosing vancomycin, especially in patients with renal impairment.
New Standard TPN Available for After Hours
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The solutions (one central; one peripheral) contain 4.25% Travasol, Dextrose 25% or 4.25% Travasol, Dextrose 5%. Standard Electrolytes contained within include:

- Sodium 70mEq/L
- Magnesium 10mEq/L
- Chloride 70mEq/L
- Sodium Bicarbonate as stabilizer - 3mEq/L

A total of one liter is contained in each bag. The solutions contain no multivitamin or trace element additives. Because the solutions are premade and prelabeled, no modifications or additions are permissible. If the solution is not acceptable for the patient, D10W will have to be used or an acceptable solution will be prepared the next day.

News from the Pharmacy

New Atrium Substation Hours
The Pharmacy Substation in the Atrium Pavilion has extended its hours from 5PM to 11:00PM. The substation will provide all pharmacy services to the patients in the Atrium Pavilion from 8:30AM to 11:00PM, 7 days a week, rather than the central pharmacy. The Evans substation will continue to close at 5PM.

Northeastern Faculty Position Open
Kimberley Adler, Pharm.D., who was the faculty member for the Northeastern University College of Pharmacy and preceptor for the students who underwent clinical clerkships at UH, resigned recently to pursue a career in the pharmaceutical manufacturing industry in Philadelphia. The college is currently recruiting a replacement for her position as well as another person to train students in the ambulatory clinics.

New Pharmacy Manager Hired.
Dan Dobson was recently promoted from pharmacist specialist to Pharmacy Manager. Dan fills a position recently vacated by Dan Showstack. Dan will assume the responsibilities previously held by Greg Aldridge, being responsible for services on the substations and clinical services, Greg will assume Dan Showstack's old responsibilities in the central pharmacy.

Anti-Drug Abuse Poster Contest a Success
The Department of Pharmacy recently sponsored an anti-drug abuse poster contest for 4th graders in the Boston City School DECIDE program. An awards ceremony was held on May 31st, with Lt. Gov. Evelyn Murphy and former Celtics M.L.Carr in the Atrium Pavilion, giving 16 prizes ranging from a personal computer to savings bonds. Prizes were donated by pharmaceutical manufacturers and local businesses. The posters are on display until June 10. The winning poster will be used by the Governor's Alliance Against Drugs for their brochures next year.

P&T Committee Actions
February/March 1988

Additions to Formulary

- Chlorhexidine Gluconate 1%

Zidovudine (Retrovir) Previously called AZT
100mg capsules

Miscellaneous
Decided to change policy requiring that all medication and IV orders be rewritten every 7 days to every 14 days, with same exceptions as before (e.g. narcotics, antibiotics, etc.).