University Hospital Pharmacy Update: October 1986 v. 1, no. 3

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Boston University
Effective Friday October 17, 1986, the Outpatient Pharmacy Services will be permanently closed and the Hospital's Outpatient Pharmacy license turned into the state. All UH Prescription files will be transferred to the Rix/Dunnington Pharmacy on the ground floor of the Doctor's Office Building as part of an agreement with Rix/Dunnington to take over the UH Employee Drug Prescription Program. Employees of University Hospital will receive many benefits from the transfer of this service including:

1. **Essentially the same or lower prices than before**
   In many cases, Rix/Dunnington will offer lower prices due better volume purchasing power.

2. **Extended hours of service**
   Prescriptions can now be filled from 8AM to 6PM, Monday through Friday, and from 9AM to 2PM on Saturdays.

3. **More convenient methods of payment**
   Rix/Dunnington will accept payment by cash, check or credit card (Visa/MC) among others.

4. **Easier Refills**
   Refills for prescriptions originally purchased at the DOB Rix/Dunnington can be refilled (if authorized) at any of 30 Rix/Dunnington stores in Eastern Massachusetts at the same discount.

Employees will be able to have authorized refills for prescriptions originally filled at the H-2 pharmacy refilled at the Rix/Dunnington DOB store. The H-2 pharmacy will not longer fill outpatient prescriptions for any reason. The outpatient window will be used exclusively for handling departmental medication requisitions. For further details, contact the Pharmacy at Extension 8790.

The Department of Pharmacy reconstitutes cytotoxic cancer chemotherapeutic agents as well as prepare intravenous admixtures of such agents in a special environment that not only protects the operator from exposure to these agents but protects the patient from bacterial contamination.

All orders for cancer chemotherapy should be written on a special antineoplastic medication order sheet (available at the nursing units). The physician should specify the medication ordered, dose/BSA, total dose, route of administration, and administration schedule. A special comments section is available to indicate such items as fluid restriction and requests for special diluents (e.g. for intrathecal use). Standard volumes and diluents will be used unless otherwise indicated.

The Pharmacy prepares chemotherapy doses **only** three times a day - 10AM, 4PM, and 10PM. Orders received between 6PM the previous day and 7AM will be delivered at 10AM. Orders received between 7AM and 12 Noon will be ready at 4PM. Orders received between 12 Noon and 6PM will be available on the floor at 10PM. This leadtime is needed for the operator and equipment to be prepared and because of the limited staffing in the pharmacy available for this function. Because of this, exceptions to these procedures cannot be generally accommodated. Your cooperation in following these procedures is appreciated.

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Current Information on Drugs:
A Review of Vancomycin Dosing in Adults
By: Daniel Dobson, M.S.C.H., R.Ph., Pharmacist

The antibiotic vancomycin can be used to treat many serious infections caused by Gram positive organisms, especially if penicillins or cephalosporins cause hypersensitivity reactions or fail to eradicate the bacteria. Although released for use in patients many years ago, the drug did not gain much popularity due to the high incidence of side effects, particularly nephrotoxicity, ototoxicity and phlebitis, while the relatively non-toxic antistaphylococcal penicillins (methicillin, nafcillin, & oxacillin) became the standard of treatment of penicillin-resistant Staphylococcus aureus infections. In the past two to three years, parenteral vancomycin has gained tremendous renewed interest due primarily to two facts: the reduction of side effects as a result of improved purity of the product and better administration guidelines; and the growing development of methicillin-resistant Staphylococcus aureus strains in the hospital environment. The increased use of vancomycin has made it the number one drug (in terms of dollars spent) at University Hospital.

While nephrotoxicity has been reduced due to increased purification of the product and phlebitis & "red neck syndrome" (fever, chills, paresthesia, erythema at the base of the neck and upper back) reduced by improved administration guidelines, ototoxicity still can remain a problem if improperly dosed. Ototoxicity has been found to be related to serum drug concentrations greater than 60-80 mcg/ml and is rarely seen with serum concentrations below 30 mcg/ml. It has been suggested that proper dosing according to pharmacokinetic principles can reduce the incidence of ototoxicity.

Renewed clinical interest in vancomycin has necessitated more precise guidelines for vancomycin dosing; however, the most practical pharmacokinetic model for dosing in adults remains a controversial subject. The routine use of 500 mg every six hours, or 1 gram every twelve hours in all patients, regardless of age, weight and kidney function is no longer considered appropriate. As with any drug that is primarily eliminated by the kidney, the dose and frequency of administration of vancomycin should be adjusted for each patient according to degree of renal function and the most recent vancomycin levels.

<table>
<thead>
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<th>Table One</th>
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<tr>
<td><strong>Estimation of Lean Body Weight (L.B.W.)</strong></td>
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<tr>
<td>Males: 50kg + 2.3 (height in inches-60)</td>
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<tr>
<td>Females: 45.5kg + 2.3 (height in inches-60)</td>
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| **Estimation of Creatinine Clearance (CrCl)** |
| Males: **CrCl = 140-age x L.B.W. in kg** |
| Serum Creatinine (SrCr) x 72 |
| Female: **CrCl = CrCl (males) x 0.85** |

*An assumption here is that kidney function is at steady state. If not, estimation of CrCl by this equation is not valid. A better approximation of CrCl would be a 24 hour urine collection.*

One of the more frequently used pharmacokinetic dosing models is Matzke's nomogram, which facilitates the determination of a dosing frequency (t) following an initial loading dose of 25mg/Kg of actual body weight (A.B.W.). To use this nomogram, estimation of lean body weight (L.B.W.) and creatinine clearance (CrCl) are necessary (see Table One).

It is well known that clearance of vancomycin and clearance of creatinine are highly correlated in patients with varying degrees of renal function. It is still unclear whether this correlation can be applied to patients on hemodialysis or peritoneal dialysis.

Once CrCl has been determined, the dosing frequency can be determined by using the Matzke nomogram (see Table Two). The intent of the nomogram is to assist in the determination of an initial dosing interval after a maintenance dose (19mg/kg of L.B.W.) has been determined. This nomogram also helps determine a new dosing interval should CrCl change during the course of therapy. Calculated vancomycin doses should be rounded off to the nearest multiple of 250mg for economy and ease of pharmaceutical manufacturing. The most recent peak and trough vancomycin levels can help determine whether to round off up or down when determining a new maintenance dose.

The following is an example of use of the Matzke nomogram. The patient is a 71 year old female admitted from a nursing home with suspected staphylococcal sepsis. Weight is 60kg, height is approximately 5 feet 4 inches.
Serum creatinine on admission is 2.1mg/dl.

a. Initial dose is 25mg/kg or 1500mg.
b. L.B.W. = 45.5kg + 2.3 (64-60) = 54.7kg
c. CrCl = 0.85 x (140-71 x 54.7kg)/2.1 x 72 = 21.2 or 21ml/min.
d. Maintenance dose = 19 x 54.7kg = 1039.3mg or rounded off = 1gm.
e. Dosing frequency, based on the Matske nomogram will be approximately every 2-2.5 days. Assuming this patient to be dehydrated on admission, a dosing interval of every two days (q48h) would be appropriate.

The protocol of the Matzke nomogram must be followed carefully. For our hypothetical patient, it may seem safer or more convenient to administer the 1gm maintenance dose as 500mg q24h. However, this nomogram has been successful in maintaining serum vancomycin concentrations of approximately 30mg/L (peak) and 7.5mg/L (tough). An alteration of dose and frequency to 500mg every twenty-four hours would reduce the desired peak and have the potential of altering therapeutic outcome. It is important to note that the nomogram can also be used to adjust dosing interval if the patient's kidney function should change during the course of therapy. For example, hydration alone could easily change our hypothetical patient's serum creatinine of 2.1mg/dl by hospital day 2 or 3, necessitating the calculation of a new estimated CrCl and the changing of the dosing interval.

This nomogram is not meant to be used for patients on peritoneal dialysis, but it can be used to aid in the initiation of vancomycin therapy for functionally anephric patients on hemodialysis. In such patients, adjustments in subsequent maintenance doses and dosing intervals should be guided by daily determination of vancomycin serum concentrations.

Another nomogram was developed by Moellering et al. and has recently been included in the manufacturer's package insert. The major difference between Moellering's and Matzke's nomograms is that Moellering's method decreases the dose while keeping the dosing interval at 24 hours, while Matzke's method increases the dosing interval while keeping the dose constant, permitting better peak concentrations and less administration costs than Moellering's method. Both methods have been found to be equally effective in terms of clinical outcome. The usefulness of vancomycin levels in the determination of a patient's ability to eliminate the drug can not be overlooked. As with any renally eliminated drug, therapeutic failures and systemic toxicities can occur when serum drug levels are drawn immediately prior to the next dose. The appropriate time to draw the peak serum level of vancomycin however, remains controversial. It is recommended that peak levels be drawn one hour after the end of a one-hour infusion.

Pharmacokinetic studies have shown that at this point, the distribution phase of the most recent infusion has ended and the elimination phase has begun. It levels of greater than 40-50mg/L are obtained during the distribution phase they will most likely not result in toxicity and should be of little concern. However, peak levels of greater than 40-50mg/L drawn one hour after a one-hour infusion, are of concern, and warrant at least a reduction in dose and an assessment of SrCr and dosing interval. Normal vancomycin serum levels are 30-40mg/L (peak) and 5-10mg/L (tough). However, it should be noted that initial toxicity studies conducted by the manufacturer had peak levels drawn 3-4 hours after the dose.

In patients who have not received an initial loading dose, serum levels should not be drawn until approximately four half-lives of the drug have elapsed. Vancomycin's half-life varies from 6-9 hours in the normal patients to as much as 6-10 days in the anuric patient. If, however, the patient has been loaded, peak and trough levels can be drawn as soon as the first and second maintenance doses respectively.

Administration of vancomycin should follow established protocols. Doses of 500mg and 1000mg are generally placed in 100 and 250ml of D5W or N.S. respectively, and infused over no less than sixty minutes (or no faster than 15mg/min5). Our hypothetical patient's loading dose therefore should have been infused over 100 minutes. Too rapid infusion of vancomycin can cause hypotension or histamine release. The latter consists of an

Figure 1: Vancomycin Dosing Nomogram from Matzke et al.3

[Diagram of the vancomycin dosing nomogram with the following information:

- **VANCOMYCIN DOSE**
  - Dosing Nomogram
  - Initial dose of 25mg/kg followed by 19mg/kg every 12 hours (determined from nomogram) should maintain serum concentrations of 30mg/L peak and 7.5mg/L trough.

- **DOSE INTERVAL (h)**
  - 12h, 24h

- **CREATININE CLEARANCE (ml/min)**
  - 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100

Dosing Nomogram for vancomycin in patients with various degrees of renal function. The nomogram is not valid for peritoneal dialysis patients.]


erythema multiforme-like rash involving the face, neck, upper trunk and upper arms, and sparing the rest of the body. In the fluid restricted patient concentrated solutions of vancomycin can be administered; however, these should be infused only through a central line to prevent vascular damage. Such solutions should not exceed a concentration of 50mg/ml and should be infused over a period of one hour, or at a rate not greater than 15mg/min.

The use of the pharmacokinetic principles described above in patients with renal impairment can not only potentially reduce the occurrence of ototoxicity resulting from vancomycin, but can result in tremendous cost savings to the institution. Certainly, the use of this method of dosing makes a lot of sense and should be encouraged.

References:

Additional References Available Upon Request

Pharmacy & Therapeutics Committee Decisions
Meeting of September 1986

A. Additions to the Formulary
1. Labetolol Intravenous (Normodyne, Trandate)
   Restricted to Use in Critical Care Units and the Operating Room Only.
2. Glipizide (Glucotrol)

B. Denied Addition to the Formulary
Buprenorphine (Buprenex)

C. Determined to be Therapeutic Equivalents
Ticarcillin/Mezlocillin
Cefotaxime/Ceftizoxime/Ceftriaxone

The Committee reaffirmed its prior decision that cefazolin and cephalothin are therapeutic equivalents and that cephalothin can be dispensed in all cases for cefazolin provided the dosing interval is changed appropriately.

D. Policies Approved
A policy of the Committee to not review requests for addition to the Formulary of drugs previous denied addition within the past 6 months was approved.

E. Proposed Deletions from the Formulary
The Committee requests comments about the proposed deletion of the following drugs from the Formulary:
Acetohexamide (Dymelor)
Chlorthiazide (Diuril)
Diazoxide (Hyperstat)
Ethacrynic Acid (Edecrin)
Guanethidine (Ismelin)
Isoxsuprine (Vasodilan)
Metaraminol (Aramine)
Methylothiazide (Enduron)
Nylidrin (Aridin)
Papaverine (Pavabid)
Pentaerythritol tetradiinitrate (Peritrate)
Triamterene (Dyrenium)
Trimethaphan (Arfonad)

F. Miscellaneous
A new form for requesting an addition of a drug to the Formulary was approved.

Definitions for Formulary Drug Categories:
I. General Use Drugs
II. Monitored Drugs (P&T Form Required)
III. Restricted Drug (Approval Required)
were rewritten to include all drugs rather than just antibiotics.