PEDIATRIC PHARMACOTHERAPY

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VANCOMYCIN: OLD CONTROVERSIES AND NEW ISSUES

Vancomycin

News From the FDA

Pharmacology Reviews

Vancomycin was isolated from a soil sample in 1956. By 1958, it was being given to adults for the treatment of gram-positive bacterial infections [1,2]. The first report of vancomycin use in children was published the following year.3 Although its importance was overshadowed by the development of the cephalosporins and extended-spectrum penicillins during the 1960's, vancomycin reemerged in the

1980's as a vital component of treatment regimens for methicillin-resistant staphylococcal strains (MRSA/MRSE).
As we approach the year 2000, vancomycin has again come to the forefront with reports of the development of bacterial resistance. In addition, recent publications have renewed interest in examining both the efficacy of our current dosing strategies and the utility of routine monitoring of serum vancomycin concentrations in clinical practice.

Finding the Optimal Dose

In 1980, Schaad, McCracken, and Nelson [4] published the results of vancomycin administration in 55 children. The authors performed a pharmacokinetic analysis in all of the children and evaluated the efficacy of vancomycin therapy in a subgroup of 12 children with documented staphylococcal disease. A dose of 30 mg/kg/day provided adequate bactericidal serum concentrations in the 7 infants studied, while a dose of 40 mg/kg/day was used for treatment of the 5 older children. A higher dose of 60 mg/kg/day was suggested for treating CNS infections. The authors recommended that therapy be adjusted to achieve peak vancomycin serum concentrations of 25-40 mcg/ml and serum bactericidal titers of at least 1:8. These recommendations, along with those from Spears and Koch [3], have become the source of our current dosing and monitoring standards. Since then, numerous publications have described the use of vancomycin in pediatric patients, but few have addressed the issue of the appropriateness of our dosing regimens in this population [2,5,6].
Recently, Chang and colleagues [7] evaluated vancomycin requirements in 28 children with cancer, ages 9 months to 13 years. All patients initially received a dose of 40 mg/kg/day. Dosing regimens were adjusted according to serum vancomycin concentrations. The authors found that an average total daily dose of 75+22 mg/kg/day was necessary to obtain desired serum concentrations of 20-40 mcg/ml for peaks and 5-15 mcg/ml for troughs. A majority of the patients (75%) required doses greater than the 60 mg/kg/day maximum recommended by Schaad's group. Based on these results, the authors have proposed that therapy should be initiated with a dose of 60 mg/kg/day divided every 6 hours in pediatric patients with cancer who have normal renal function. The authors did not examine why the patients required such high doses, nor did they study a control group of children without cancer. Interestingly, the endpoint of dose adjustment in this study was based on serum vancomycin concentrations alone. Individual MIC and MBC data were not evaluated; it is not known whether lower doses would have been adequate for the treatment of these children.

Therapeutic Drug Monitoring (TDM)

Although an accepted practice by most clinicians, the value of routine therapeutic drug monitoring has been called into question [8-10]. TDM is designed to serve

two purposes: ensure efficacy and identify potential toxicities. It is beneficial only when there is a definable relationship between serum concentrations and therapeutic endpoints. In a paper published last year, Cantu and colleagues [9] addressed the relative lack of data available which substantiate a correlation between vancomycin efficacy and serum concentrations. In addition, they note that the true frequency of vancomycin-induced nephrotoxicity and ototoxicity is not well defined and that TDM has not demonstrated a significant ability to avoid these adverse events.

As we attempt to provide the most cost-effective medical therapy for our patients, the benefit of obtaining serum concentrations must be better documented. Few prospective, controlled studies have been performed to evaluate the efficacy of TDM. In 1994, Welty and Copa [11] compared the outcomes in 61 adults who were managed by an established TDM consultation service versus 55 patients who were monitored empirically. The authors found no significant differences in efficacy between the two groups. They did however, report that fewer of the patients followed by the TDM consultation service experienced renal insufficiency, as defined by a reduction in creatinine clearance. Although not statistically significant, the TDM-consult group also tended to have a shorter length of therapy and hospitalization. Just last month, Zimmerman and colleagues [12] reported that patients who had serum concentrations within the therapeutic range were afebrile sooner and had a faster return of their white cell counts to normal, compared to patients with lower vancomycin levels. No differences in morbidity or development of adverse effects were noted. At this time, no comparative trials have been performed in pediatric patients.

Based on this limited information, it is reasonable to question of the value of routine vancomycin TDM. Empiric methods based on age, weight, and renal function alone may be adequate for determining dosing regimens. While some institutions have moved to eliminate all vancomycin TDM [11,13], a conservative approach may be more appropriate at the present time. In an editorial accompanying the article by Cantu's group, Moellering [14] identified patients in whom the measurement of serum concentrations would be most beneficial. This list has also been recommended for application to pediatric patients by Nelson and McCracken [15]. These authors advocate the use of vancomycin TDM for:

- patients receiving concomitant therapy with another known nephrotoxin (e.g. aminoglycosides)
- patients with renal failure, including those on dialysis
- patients with changing renal function, including premature neonates
- patients receiving large doses, such as those being treated for meningitis

Routine TDM services require the time of lab, pharmacy, and medical personnel, as well as the expense of obtaining and analyzing the serum samples. These recommendations may allow us to focus on those patients who would most benefit from this additional use of resources. However, it is likely that the debate surrounding this issue will continue until more research has been done.

Vancomycin-Resistant Enterococci (VRE)

Another topic receiving a great deal of attention has been the development of gram-positive bacterial strains that are resistant to most common antibiotics, including vancomycin. In 1988, investigators from both the United Kingdom and France reported isolation of vancomycin-resistant enterococcal strains. Since that time, the problem has spread worldwide. The CDC has documented a dramatic increase in vancomycin-resistant bacterial strains in the US, from a cumulative incidence of 3.1% from 1989-1992 to 13.6% in 1993. The mortality associated with VRE infection has been estimated at 55% [16].

As of December 1994, VRE had been isolated from the cultures of 56 patients within the UVa Medical Center. Of these, nine cases involved VRE infection. Cases of VRE have been reported within the Children's Medical Center, although the number remains significantly less than that seen in other areas of the hospital. VRE is believed to originate with the colonization of the stool in patients receiving oral vancomycin. The organism is spread rapidly by personal contact and the contamination of work surfaces. Risk factors for the development of VRE infection include: prior vancomycin therapy (including both oral and parenteral use), prolonged hospitalization (> 6 weeks), neutropenia, the use of invasive procedures, and the co-administration of a third-generation cephalosporin [16].

There are few treatment options for VRE. The quinolones and tetracyclines have been used successfully, in combination or with additional agents such as gentamicin or rifampin. Several investigational agents which may be useful in treating VRE are being studied. Teicoplanin is a glycopeptide antibiotic, similar in spectrum to vancomycin. It has been available in Europe for several years, but has not yet been released in the US. Teicoplanin has been used to treat gram-positive infections in children, with doses of 6-10 mg/kg/day [17]. Due to the similarities of their chemical structures, cross-resistance to teicoplanin in patients with VRE is not unexpected and has been reported in clinical use.

Other agents under investigation which may be useful for treating VRE include everinomycins, glycylglycines (derivatives of minocycline), and streptogramins (similar to the macrolide antibiotics). Synercid® is a combination of two streptogramins, quinupristin and dalfopristin. It is the first of these agents to be available in the US by compassionate-use protocol. Synercid® has been used successfully to treat one adult patient with VRE in our institution.

The key to preventing infection lies in minimizing the spread of VRE. Limiting the use of vancomycin and maintaining appropriate isolation procedures are important components in managing this problem. The UVa Infection Control Committee has recommended restricting vancomycin use to the following situations:

- treatment of serious infections due to beta-lactam resistant gram-positive organisms

- treatment of infections due to gram-positive organisms or surgical prophylaxis in patients with serious allergy to beta-lactam antibiotics
- treatment of serious laboratory-documented C. difficile colitis failing to respond to metronidazole
- prophylaxis for endocarditis as recommended by the American Heart Association guidelines
- surgical prophylaxis for procedures involving implantation of prosthetic materials, if a high rate of MRSA/MRSE infection is known to occur with cefazolin
- treatment of infections due to gram-positive organisms in premature neonates
- intravitreal administration during surgery

On-going surveillance for outbreaks of VRE is being performed by the Infection Control Committee as well as analysis of our patterns of vancomycin use. It is hoped that these measures will prevent VRE from becoming a significant problem within our patient population. Until that time, vancomycin will remain an important part of therapy for children with bacterial infections.

References

1. McHenry MC, Gavan TL. Vancomycin. Pediatr Clin North Am 1983;30:31-47.
2. Wandstrat TL, Phelps SJ. Vancomycin dosing in neonatal patients: The controversy continues. Neonatal Network 1994;13:33-9.
3. Spears RL, Koch R. The use of vancomycin in pediatrics. Antibiot Ann 1959-1960:798-803.
4. Schaad UB, McCracken GH, Nelson JD. Clinical pharmacology and efficacy of vancomycin in pediatric patients. J Ped 1980;96:119-26.
5. Alpert G, Campos JM, Harris MC et al. Vancomycin dosage in pediatrics reconsidered. AJDC 1984;138:20-2.
6. Pryka RD, Rodvold KA, Erdman SM. An updated comparison of drug dosing methods. Part IV: Vancomycin. Clin Pharmacokinet 1991;20:463-76.
7. Chang D, Liem L, Malogolowkin M. A prospective study of vancomycin pharmacokinetics and dosage requirements in pediatric cancer patients. Pediatr Infect Dis J 1994;13:969-74.
8. Freeman CD, Quintiliani R, Nightingale CH. Vancomycin therapeutic drug monitoring: Is it necessary? Ann Pharmacother 1993;27:594-8.
9. Cantu TG, Yamanaka-Yuen NA, Lietman PS. Serum vancomycin concentrations: Reappraisal of their clinical value. Clin Infect Dis 1994;18:533-43.
10. Pryka RD. Vancomycin serum concentration monitoring: A continued debate. Ann Pharmacother 1994;28:1397-9.
11. Welty TE, Copa AK. Impact of vancomycin therapeutic drug monitoring on patient care. Ann Pharmacother 1994;28:1335-9.
12. Zimmerman AE, Katona BG, Plaisance KI. Association of vancomycin serum concentrations with outcomes in patients with gram-positive bacteremia. Pharmacotherapy 1995;15(1):85-91.

13. Reed MD, Farrar HC, Marx CE et al. Monitoring serum vancomycin concentrations: to be or not to be! Clin Pharmacol Ther 1993;53(2):149. [Abstract].
14. Moellering RC. Editorial: Monitoring serum vancomycin levels: climbing the mountain because it is there? Clin Infect Dis 1994;18:544-6.
15. Nelson JD, McCracken GH. Monitoring vancomycin concentrations. Pediatr Infect Dis Newsletter 1994;20(7):13-4.
16. Spera RV, Farber BF. Multidrug-resistant Enterococcus faecium: an untreatable nosocomial pathogen. Drugs 1994;48:678-88.
17. Wilson APR, Gruneberg RN, Neu H. Dosage recommendations for teicoplanin. J Antimicrob Chemother 1993;32:792-6.

News from the FDA

The following drugs were approved by the FDA at the end of 1994:

- Abciximab (ReoPro®) - antiplatelet therapy designed to reduce complications following angioplasty
- Dalteparin (Fragmin®) - another low-molecular weight heparin for preventing/minimizing
- DVTDorzolamide (Trusopt®) - for treatment of open angle glaucoma
- Fluvoxamine (Luvox®) - a serotonin reuptake inhibitor for treatment of depression and obsessive-compulsive disorder, similar to Prozac®
- Lamotrigine (Lamictal®) - an anticonvulsant for partial seizures, data available on pediatric use
- Metformin (Glucophage®) - oral antihyperglycemic for treatment of Type II diabetes
- Nefazodone (Serzone®) - an antidepressant
- Rimexolone (Vexol®) - for treatment of uveitis
- Spirapril (Renormax®) - another ACE inhibitor for hypertension
- Vinorelbine (Navelbine®) - chemotherapy for non-smallcell lung cancer

In addition, there are a number of new medications that are candidates for approval during 1995 that may be useful in pediatric patients. The following is a partial list of agents which have been recommended for approval by one of the FDA advisory committees:

- Amiodarone (Cordarone IV®) - will be available for intravenous use
- Cefaclor (Ceclor CD®) - a longer-acting preparation for twice daily dosing
- Cefipime (Maxipime®) - an anti-Pseudomonal cephalosporin
- Dirithromycin (Dynabac®) - another macrolide antibiotic
- Hepatitis A vaccine (Harvix®)
- Ipratropium/Albuterol (Combivent®)
- Tuberculosis vaccine (Mycobax®)

- Varicella vaccine (Varivax®) - finally?

After the patent on a medication expires, generic formulations can be marketed. The following agents became available in generic form during 1994:

- Bumetanide (injection)
- Cefaclor (oral suspension)
- Cimetidine (injection, oral solution, and tablets)
- Cromolyn (inhalation)
- Etoposide (injection)
- Flurbiprofen (tablets)
- Glipizide (tablets)
- Lorazepam (injection)
- Naproxen (oral suspension)
- Triazolam (tablets)
- Verapamil (sustained-release tablets)

Pharmacology Literature Review

Autism Therapies
This brief review focuses on the available medical therapies for the management of children with autism and other pervasive developmental disorders. Although the pathophysiology section may not be needed by those who provide care for these children, I recommend this article for its diagrams of neurotransmitter-drug relationships. In addition, the authors have included a concise table of the drugs and their appropriate dosages (Gilman JT et al. Autism and associated behavioral disorders: Pharmacotherapeutic intervention. Ann Pharmacother 1995;29(1):47-56).

Caffeine Review
Although only a small section is devoted to the treatment of apnea of prematurity, this review provides an excellent source of information on the mechanism of action and adverse effects of caffeine administration. This paper also includes a brief discussion of the proposed mechanisms of tolerance and adaptation (Sawynok J. Pharmacological rationale for the clinical use of caffeine. Drugs 1995;49(1):37-50).

Fluconazole Kinetics
The pharmacokinetics of fluconazole were studied in 10 immune-compromised children. A single 6 mg/kg IV dose was given, followed by seven 3 mg/kg oral doses. Oral bioavailability was 92% and the mean volume of distribution was

0.77+0.12 L/kg at steady state. The average distribution half-life was 1.67+1.25 hours; elimination half-life was 15.62+3.21 hours. The authors concluded that children have a larger volume of distribution than adults and a more rapid elimination (Seay RE et al. Pharmacokinetics of fluconazole in immune-compromised children with leukemia or other hematologic disease. Pharmacotherapy 1995;15(1):52-8).

G-CSF Binding to Catheters

The amount of drug lost when filgrastim (G-CSF) is administered without albumin through a silicone rubber catheter was evaluated in an effort to simulate use in children with central venous lines. More than 10% of the initial dose was lost as a result of binding to the catheter surface. Drug loss became insignificant with subsequent doses, most likely due to the coating effect of the first dose. Biological activity was not affected. (McCullough JM et al. Recovery and biological activity of filgrastim after injection through silicone rubber catheters. Am J Health-Syst Pharm 1995;52:186-8).

Isoniazid in Children

The production of hydrazine, a hepatotoxic metabolite, was studied in 32 children with tuberculous meningitis receiving isoniazid. All children were evaluated at 1 month; fourteen of the children were followed for up to 6 months. Significant levels of hydrazine were seen at one month, but had declined by 6 months. None of the children experienced hepatic disease. The authors hypothesize that additional risk factors, such as preexisting liver damage, must be present for hydrazine to cause toxicity. (Donald PR et al. Hydrazine production in children receiving isoniazid for the treatment of tuberculous meningitis. Ann Pharmacother 1994;28(12):1340-3).

Midazolam in Neonates

The pharmacokinetic profile of midazolam was evaluated in 187 neonates. The average volume of distribution was 0.9+0.07 L/kg. Clearance (mean = 0.07+0.01 L/kg/hr) was directly proportional to birthweight and gestational age. The authors concluded that neonates should receive lower doses of midazolam than those currently recommended based on studies done in older infants. This study was performed with NONMEM analysis and may be difficult reading for those unfamiliar with this computer modeling technique. (Burtin P et al. Population pharmacokinetics of midazolam in neonates. Clin Pharmacol Ther 1994;56:615-25).

Ondansetron for Outpatient Use

The efficacy of a 2-dose ondansetron regimen was studied in 16 children, ages 2-15 years, with leukemia. A patient/parent survey was used to collect data. Ondansetron was completely effective (no nausea/vomiting) in more than 50% of the patients surveyed. The authors concluded that this regimen was adequate for most children. (Holdsworth MT et al. Assessment of chemotherapy-induced

emesis and evaluation of a reduced-dose intravenous ondansetron regimen in pediatric outpatients with leukemia. Ann Pharmacother 1995;29(1):16-21).

New Anticonvulsants

This review focuses on gabapentin and lamotrigine, two recently marketed anticonvulsants. Gabapentin has not been evaluated in the pediatric population. Lamotrigine, however, appears to be an effective add-on therapy for children with refractory partial seizures. It has also been used to treat children with Lennox-Gastaut syndrome. Dosing and monitoring guidelines are included. (Btaiche IF et al. Gabapentin and lamotrigine: Novel antiepileptic drugs. Am J Health-Syst Pharm 1995;52:61-9).

Oral Rehydration Therapy

This is a thorough review of the use of oral rehydration therapy in the treatment of children with acute diarrheal disease. The rationale for inclusion of each component is discussed. In addition, the authors present other clinical situations where this therapy may be appropriate, such as short bowel syndrome. (Farthing MJG. Oral rehydration therapy. Pharmac Ther 1994;64:477-92).

Recent Advances

This is a very short review article designed to bring those unfamiliar with the field of developmental pharmacology up to date. Topics include: nitric oxide for persistent pulmonary hypertension, perfluorocarbons for RDS, vitamin E administration to improve cyclosporin absorption, as well as new developments in antiemetic therapy, treatment of hypercholesterolemia, and vaccinations. (Gal P et al. Recent advances in pediatrics. Ann Pharmacother 1995;29(1):66-70).

Theophylline Depresses Vitamin B6

Vitamin B6 levels were determined in 20 asthmatic children receiving chronic theophylline therapy. A significant reduction in B6 was observed when compared with a control group of six asthmatic children not on theophylline. The mechanism of this effect may involve an inhibition of hepatic synthesis or stimulation of urinary elimination. Further studies are needed to assess the clinical significance of this effect and the need for replacement therapy. (Shimizu T et al. Theophylline attenuates circulating vitamin B6 levels in children with asthma. Pharmacology 1994;49:392-7).

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee on 1/27/95:

1. Glucotrol, an extended release preparation of glipizide was added to the formulary. Glipizide is an oral sulfonylurea used in the treatment of Type II diabetes.
2. A new preparation of BCG (TheraCys) was approved for use in the treatment of bladder cancer.
3. Colestipol (Colestid) tablets were added to the formulary. This should be much more palatable to older children than the slurry made from mixing the powder with water. We will continue to have the powder available.
4. Hemin injection (Panhematin) was approved for the treatment of intermittent porphyria.
5. Dinoprostone/PGE2 (Prepidil) was also added to the formulary. The gel is placed on the cervix to ripen it for induction of labor. Intrauterine fetal sepsis and amnionitis have been reported with dinoprostone use, but appear to be rare. Fetal status must be monitored closely when this product is used since it also acts as an oxytocic.

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