PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the University of Virginia Children's Hospital

Volume 14 Number 2 February 2008

Use of Clindamycin in Pediatric Infections

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Clindamycin is a semisynthetic derivative of lincomycin developed in the mid-1960's. Since its introduction, it has become a standard therapy for the treatment of anaerobic infections and is often used to treat Gram positive infections in patients allergic to beta-lactam antibiotics.[1] More recently, clindamycin has become an important component in the treatment of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections. This issue of *Pediatric Pharmacotherapy* will provide a basic review of the pharmacology of clindamycin and highlight several new papers describing its use in treating pediatric infections.

Mechanism of Action/Antimicrobial Spectrum

Clindamycin reversibly binds to the 50S subunit of bacterial ribosomes preventing peptide bond formation, resulting in inhibition of bacterial protein synthesis. It is bacteriostatic against a variety of Gram positive aerobic and anaerobic organisms, as well as some Gram negative anaerobes and protozoa.[1-3] Clindamycin has demonstrated both *in vitro* and *in vivo* evidence of activity against the following organisms:

Gram positive aerobes
Staphylococcus aureus
Streptococcus pneumoniae
Strep pyogenes

Anaerobes
Clostridium perfringens
Fusobacterium necrophorum
Fusobacterium nucleatum
Peptostreptococcus anaerobius
Prevotella melaninogenica

In addition, clindamycin has been shown to have *in vitro* activity against the following organisms:

Gram positive aerobes
Bacillus spp
Corynebacterium diphtheriae
Nocardia spp
Strep agalactiae
Strep anginosus
Strep mitis
Strep oralis
Strep viridans

Anaerobes
Actinomyces israelii
Bacteroides spp
Bifidobacterium spp
Clostridium clostridioforme
Eubacterium lentum
Finegoldia magna
Micromoas micros
Prevotella bivia
Prevotella intermedia
Propionibacterium acnes

Clindamycin has also been shown to be effective in the treatment of *Chlamydia trachomatis* and *Gardnerella vaginalis* infections in women as well as *Helicobacter pylori* infections.[2] In addition to its antibacterial effects, clindamycin may also have immunomodulating effects. In laboratory studies, it reduces bacterial adhesion to mucosal surfaces and facilitates white blood cell chemotaxis, opsonization, and phagocytosis. Clindamycin may also inhibit production of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1β (IL-1β), and inducible nitric oxide, while increasing levels of IL-6.[1,4]

Clindamycin may also be useful in the treatment of protozoal infections, where it appears to interrupt target protein synthesis in the apicoplast, a parasite-specific organelle necessary for survival. Susceptible organisms include *Toxoplasma gondii*, *Babesia* spp, and *Plasmodium falciparum*.[1]

Because of the increasing incidence of bacterial resistance to clindamycin,[5,6] these lists serve only

as a general guideline. Institution-specific or regional evaluations of antibiotic resistance patterns should be consulted prior to initiating therapy for serious infections.

Clinical Studies in Children

Clindamycin has been used for many years in the treatment of infections in children. It has traditionally been a component of empiric antibiotic regimens for dental, bone and joint infections where anaerobes were likely causes, as well as in the treatment of serious skin and soft tissue infections.[1-3] Clindamycin has a particular niche in the treatment of beta-lactam resistant infections. In 1952, Eagle first demonstrated the failure of penicillin to eradicate *Streptococcus pyogenes* myositis in a murine model when the antibiotic was given late in the course or in the presence of a high bacterial load.[7] This did not appear to be related to bacterial resistance, but was associated with a decreased concentration of penicillin-binding proteins in the stationary phase of growth. Subsequent research of the "Eagle effect" by Stevens and colleagues in 1988 and Zimbelman, Palmer, and Todd in 1999 showed that clindamycin was more efficacious in this setting, likely as a result of its ability to inhibit bacterial protein synthesis independent of bacterial load or the stage of bacterial growth.[8,9]

In recent years, clindamycin has emerged as a primary therapy in the management of children with CA-MRSA infections. The incidence of CA-MRSA has increased dramatically over the past decade. In a study from 1998, Herold and colleagues reported a 25-fold increase in hospitalizations for MRSA infections in previously healthy children without known risk factors.[10] Several reports have demonstrated the efficacy of clindamycin as part of combination treatment regimens in a variety of pediatric CA-MRSA infections, including cellulitis and abscesses, pneumonia, and osteomyelitis.[11-15]

In 2002, Martinez-Aguilar and colleagues at Texas Children's Hospital evaluated the records of 99 children with community-acquired invasive *Staph aureus* infections.[11] They identified CA-MRSA in 46 children and community-acquired methicillin-sensitive *Staph aureus* (CA-MSSA) in another 53. In the MRSA group, 39 received clindamycin as primary therapy, including 20 patients who received it as the sole initial drug. The other drugs used included vancomycin or a beta-lactam antibiotic. Clindamycin was used as initial therapy in 24 of the MSSA patients. The remaining patients received beta-lactam antibiotics. The median number of febrile days was 3 for the MRSA patients and 2 for the MSSA patients (p=0.07) and the median number of days with a positive blood culture was 2 for the MRSA group and 1 for the MSSA group (p=0.04). The authors concluded that clindamycin was an effective therapy for community-acquired *Staph aureus* infections in children.

Arnold and colleagues conducted a retrospective study in 2006 of 158 pediatric osteomyelitis infections between 2000 and 2004 at LeBonheur Children's Medical Center.[13] The proportion of infections caused by MSSA strains remained constant over the evaluation period (10-13%), but the incidence of MRSA rose from 4% to 40%. There were more subperiosteal abscesses in the MRSA patients than in the MSSA group (71% versus 38%, p=0.02). Ninety-one percent of the MRSA patients required surgical procedures, compared to 62% of the MSSA patients (p<0.001). Length of stay was also significantly longer in the MRSA group (10 days versus 7 days in the MSSA group, p=0.0001). Clindamycin was not routinely used in treating osteomyelitis prior to the increase in MRSA infections, but was rapidly incorporated into the institution's empiric regimen. Of the 47 MRSA isolates, 46 were susceptible to clindamycin.

Guss and Kazahaya reported a similar increase in the number of cases of MRSA lymphadenitis.[14] They conducted a retrospective study of children who underwent trans-cervical surgical drainage of lymph node abscesses between 2000 and 2006. Of the 62 children identified, 49 had positive bacterial cultures. Of the *Staph aureus* cultures, 27% were MRSA. All of the MRSA isolates were susceptible to clindamycin. The MRSA isolates all came from the second half of the study; the authors found no cases of CA-MRSA in their patient sample prior to 2003.

Clindamycin has also been found to be an effective treatment for neonates with CA-MRSA infections. In November 2007, Fortunov and colleagues published a retrospective review of community-acquired *Staph aureus* infections in previously healthy term and late-preterm neonates at Texas Children's Hospital.[15] The patients were admitted over a 5-year period between August 2001 and July 2006. Of the 126 infections, 84 were methicillin-resistant. A total of 68 patients presented with cellulitis or an abscess, 43 had pustules, and 15 had invasive disease. Empiric treatment with clindamycin was prescribed in 75% of the patients with pustules, 58% of the patients with cellulitis or abscess, and 15% of the patients with invasive infections. In the patients with proven CA-MRSA, clindamycin was used as a definitive treatment in 51%. Forty-nine neonates received oral therapy after initial

intravenous (IV) treatment. Clindamycin was the most commonly used oral antibiotic in both the methicillin-resistant and methicillin-sensitive groups. There was only one treatment failure.

Pharmacokinetics

Clindamycin is available in three salt forms: hydrochloride (oral capsules), palmitate (oral solution), and phosphate (injection). Clindamycin hydrochloride is well absorbed after oral administration, with an absolute bioavailability of 90%. In adults given a standard 150 mg oral dose, an average peak serum clindamycin level of 2.5 mcg/mL is achieved within 45 minutes. Administration with food does not appear to affect absorption.

Clindamycin is widely distributed in body fluids and tissues, including bone and pleural fluid. It does not appreciably distribute into cerebrospinal fluid, even with inflamed meninges. It is extensively metabolized via cytochrome P450 3A4 to primarily inactive compounds, with approximately 10% excreted in the urine. The average half-life in adults is 2 to 3 hours. The serum half-life may be slightly longer in patients with severe renal or hepatic dysfunction, but no specific dosing adjustment is recommended.[1-3] The half-life is also longer in neonates: approximately 4 hours in term neonates and up to 8 to 9 hours in preterm neonates.[16]

Drug Interactions

Because of its ability to reduce nicotinic receptor depolarization, clindamycin may potentiate the effects of neuromuscular blocking agents. It should be used with caution in patients requiring these drugs over a prolonged period. The combination of erythromycin and clindamycin appears to produce antagonistic effects *in vitro*, so the concomitant use of these two antibiotics is not recommended.[1-3]

Adverse Effects

Clindamycin is generally well tolerated. Common adverse effects reported with its use include anorexia, abdominal pain, nausea, vomiting, and diarrhea. Hypersensitivity reactions, including rash and urticaria, have been reported, as well as rare cases of erythema multiforme, Stevens-Johnson syndrome, and anaphylactoid reactions. Clindamycin should be used with caution in patients with an underlying gastrointestinal disease or infection and in patients with atopy.[1-,3]

Rapid IV administration of clindamycin has been associated with hypotension, arrhythmias, and cardiac arrest. Other rare adverse effects associated with clindamycin include: esophagitis, jaundice and abnormal hepatic transaminases, azotemia, oliguria, proteinuria, transient leukopenia and eosinophilia, thrombocytopenia, agranulocytosis, and polyarthritis.[2,3] Many of these rare adverse effects have been identified through case reports and a direct causal relationship with clindamycin has not been established.

As with other antibiotics, clindamycin use results in substantial changes in bowel microflora, and may result in the development of *Clostridium difficile* associated diarrhea (CDAD). Clindamycin, cephalosporins, ampicillin, and amoxicillin are the agents most frequently linked with CDAD. Because of the risk for severe colitis and reports of fatalities in patients with CDAD, prolonged systemic use of clindamycin should be reserved for severe infections when there are no alternative agents.[2,3]

Dosing Recommendations

The parenteral dose for clindamycin in children is 20 to 40 mg/kg/day divided and given IV or IM every 6 or 8 hours. In neonates, the dose should be based on both weight and age, to allow for a slower elimination. In preterm neonates less than 2 kg, a dose of 10 mg/kg/day should be divided and given every 12 hours. In neonates over 2 kg and less than 1 week of age, a dose of 15 mg/kg/day should be divided and given every 8 hours. In older neonates, a dose of 20-30 mg/kg/day may be divided and given every 6 to 8 hours.[2,3]

The recommended adult dose for parenteral clindamycin is 600 to 1,200 mg/day divided and given IV or IM every 12, 8, or 6 hours. The maximum concentration for IV administration is 18 mg/mL, and the maximum rate of infusion is 30 mg/min.[2,3]

The recommended oral dose of clindamycin in children with serious infections is 8 to 16 mg/kg/day divided and given every 6 or 8 hours. In those with more severe infections, a higher dose of 16 to 20 mg/kg/day may be used. In adults, the manufacturer recommends an oral dose of 150 mg to 300 mg every 6 hours for serious infections and a dose of 300 to 450 mg every 6 hours for severe infections. Clindamycin capsules should be taken with a full glass of water to prevent esophagitis.[2,3]

Availability

Clindamycin hydrochloride is available as brand (Cleocin HCl®; Pfizer) or generic products in 75, 150, and 300 mg capsules. A cherry-flavored oral solution of clindamycin palmitate (75 mg/5 mL) is also available, as well as an injectable

formulation of clindamycin phosphate (150 mg/mL). The injectable product contains benzyl alcohol as a preservative and should be used with caution in neonates.[2,3]

Summary

Since its development 40 years ago, clindamycin has become an important alternative in the treatment of serious Gram positive and anaerobic infections. With the increasing incidence of CA-MRSA infections in children, it will likely become a more frequent therapy in the pediatric population.

The editors wish to thank Dr. J. Owen Hendley for reviewing this article prior to publication.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 1/24/08:

1. Mycophenolate sodium (Myfortic®) was added to the Outpatient Formulary for patients with significant adverse gastrointestinal effects from mycophenolate mofetil.

2. Sodium phenylbutyrate (Buphenyl®) was added to both the Inpatient and Outpatient Formularies for the treatment of patients with urea cycle disorders.

3. A combination metered dose inhaler with budesonide, a corticosteroid, and formoterol, a long-acting beta$_2$-adrenergic agonist, (Symbicort®) was added to both the Inpatient and Outpatient Formularies. In a class review of the inhaled corticosteroids, triamcinolone (Azmacort®) was removed from the Formulary and mometasone furoate (Asmanex®) was added.

4. In an annual Formulary class review, trimethobenzamide (Tigan®) suppositories were removed from the Inpatient and Outpatient Formularies and aluminum hydroxide (Gaviscon®) was removed from the Inpatient Formulary.

5. The results of medication utilization evaluations involving rifaximin, IV promethazine, and argatroban were presented, as well as the Non-Formulary Quarterly Report.

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