PEDIATRIC PHARMACOTHERAPY

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

Volume 13 Number 9 September 2007

Retapamulin: A New Option for Impetigo

Marcia L. Buck, Pharm.D., FCCP

On April 17, 2007, retapamulin was approved by the Food and Drug Administration (FDA) for the treatment of impetigo due to *Staphylococcus aureus* or *Streptococcus pyogenes* in patients 9 months of age and older.[1,2] It is the first new topical antibiotic approved by the FDA since the release of mupirocin (Bactroban®) nearly 20 years ago. It offers several potential advantages over mupirocin, including less frequent application (twice daily instead of three times daily), a shorter treatment period (5 days rather than 8-12 days), and a reduced potential for the development of bacterial resistance. This issue of *Pediatric Pharmacotherapy* will review the pharmacology of retapamulin and the studies conducted in children and adults which led to its approval by the FDA.

Mechanism of Action

Retapamulin is a semisynthetic pleuromutilin antibiotic. Pleuromutilin derivatives interact with the 50S subunit of bacterial ribosomes at protein L3 near the peptidyl transferase center. Binding at this unique site inhibits peptidyl transferase activity and partially inhibits the binding of initiator tRNA to the P-site of the ribosome, resulting in inhibition of bacterial protein synthesis.[1-5]

While other agents in this class (tiamulin and valnemulin) have been developed as veterinary antibiotics, retapamulin is the first pleuromutilin derivative to be used in humans. Retapamulin is bacteriostatic against *Staphylococcus aureus*, with MICs between 0.03 and 0.25 mcg/mL, and *Streptococcus pyogenes*, with MICs between 0.008 and 0.03 mcg/mL.[1-5] At concentrations approximately 1,000 times the MIC, retapamulin is bactericidal against these organisms. During *in vitro* testing, Pankuch and colleagues found no differences in response to methicillin-susceptible and methicillin-resistant or vancomycin-resistant strains of *S. aureus*; however, retapamulin has not yet received FDA approval for treatment of methicillin-resistant or vancomycin-resistant pathogens.[6]

Additional *in vitro* testing has documented activity against a wide number of bacterial strains, including *Propionibacterium*, *Bacteroides*, and *Clostridium* species.[7,8] Goldstein and colleagues demonstrated in vitro activity of retapamulin against 141 *Propionibacterium* clinical isolates, including 117 isolates of *P. acnes.*[7] Among the isolates tested were seven multi-drug resistant strains, all of which were susceptible to retapamulin.

In a study published in March 2007, Odou and colleagues evaluated the in vitro activity of retapamulin against 232 anaerobes, comparing the results to those obtained with common systemic antibiotics.[8] At concentrations of 2 mcg/mL or less, retapamulin inhibited 90% of the anaerobic strains tested, compared to 98% inhibition with amoxicillin/clavulanate, and rates of 88% for metronidazole, 85% for clindamycin, and 80% for ceftriaxone.

Bacterial resistance to retapamulin has been demonstrated *in vitro* through two mechanisms: mutation in protein L3 and the development of an efflux mechanism. Mutation in L3 has been shown to be a multi-step process which appears to be slow to emerge.[4] As a result, the likelihood for target mutation during therapy is believed to be low.[5] In the clinical trials with retapamulin conducted to date, there have been no reports of the development of bacterial resistance in previously sensitive strains.[2] Because of its unique site of action, there appears to be no target-specific cross-resistance between retapamulin and other topical antibiotics.[5]

Clinical Experience

A randomized, double-blind, placebo-controlled Phase III trial of retapamulin was conducted by the manufacturer in 210 patients between 9 months and 73 years of age with impetigo.[2,9]

The majority of patients in the study (78%) were children less than 13 years of age. Patients were eligible for enrollment if they required treatment of lesions covering no more than 100 cm^2 total area (up to 10 lesions) or up to 2% total body surface area. They were randomized in a 2:1 ratio to receive either active or placebo ointment, applied twice daily for 5 days.

Evaluations were completed 2 and 9 days after the end of treatment. Clinical success was defined as the absence of lesions, dried lesions, or improvement in lesions such that no additional treatment was needed. At the post-treatment day 2 evaluation, the intention to treat analysis revealed a clinical success rate of 85.6% with retapamulin (119/139 patients) compared to 52.1% with placebo (37/71). In those patients completing the entire protocol, the response rate was 89.5% (111/124) in the treatment group compared to 53.2% (33/62) in the controls. At follow-up on post-treatment day 9, the success rate for the per protocol population was 82.4% in the retapamulin group and 43.1% in the controls.[2,9]

Eighty-two percent of the patients had culture-positive *S. aureus* or *S. pyogenes* infections. In the *S. aureus* group, the microbiologic response rate was 89.8% in the retapamulin group, compared to 52.1% in the controls at post-treatment day 2. At follow-up on post-treatment day 9, the success rates were 84.5% in the treatment group and 43.2% in the controls. In the patients with *S. pyogenes*, the success rate at day 2 was 90.6% in the treatment group and 42.9% in the controls. At follow-up on day 9, the success rates were 90.6% in the retapamulin patients and 33.3% in the controls. [2,9]

The efficacy of topical retapamulin has also been compared to oral cephalexin for secondarily infected dermatitis.[10,11] In September 2006, Free and colleagues reported the combined results of two randomized, double-blind, placebo-controlled multicenter studies.[10] A total of 1,904 adult patients received either retapamulin applied twice daily for 5 days or cephalexin 500 mg orally twice daily for 10 days. In the patients completing the protocol, 89.5% of the retapamulin group had a successful clinical response compared to 91.9% of the cephalexin group (95% confidence interval, -5.4% to 0.5%). In patients with proven *S. aureus* or *S. pyogenes* infections, the microbiological success rate was 89.2% with retapamulin group and 92.6% with cephalexin. Noncompliance, defined as missing more than 20% of doses, was documented in 8% of the cephalexin patients, compared to only 0.4% of the patients using retapamulin. The authors concluded that retapamulin was an effective alternative to systemic therapy and may be more convenient for some patients.

The results of a similar study were published in the December 2006 issue of *The Journal of the American Academy of Dermatology*.[11] Parish and colleagues conducted a comparison trial of retapamulin applied twice daily for 5 days and oral cephalexin, 500 mg twice daily, for 10 days. A total of 546 children (9 months of age and older) and adults participated in the study. At follow-up, clinical success rates were similar between the two groups: 85.9% in the retapamulin patients and 89.7% in the cephalexin patients. Microbiologic success rates were 87.2% for retapamulin and 91.8% for cephalexin. Both drugs were well tolerated, but patients preferred the ointment over the oral drug.

Pharmacokinetics

In a study conducted in healthy adults, daily application of retapamulin to either intact or abraded skin resulted in minimal systemic absorption. The median maximum plasma concentration after application to 800 cm^2 of intact skin was 3.5 ng/mL (range 1.2-7.8 ng/mL). After application to 200 cm^2 abraded skin, the median maximum serum concentration was 9 ng/mL (range 6.7-12.8 ng/mL).[2]

Evaluation of serum retapamulin plasma concentrations during clinical trials has also demonstrated minimal systemic absorption. In samples obtained from 380 adults and 136 children after twice daily topical retapamulin application, only 11% of patients had measurable levels. The median plasma concentration in these patients was 0.8 ng/mL. The maximum plasma concentrations reported were 10.7 ng/mL in adults and 18.5 ng/mL in children.[2]

Relatively little is known of the pharmacokinetic profile of retapamulin after systemic absorption. It appears to be highly protein bound (94%) and is metabolized via oxygenation and N-demethylation to a large number of metabolites. The primary metabolic pathway is through cytochrome P450 3A4 (CYP3A4).[1,2]

Drug Interactions

Administration of oral ketoconazole in patients using retapamulin can increase retapamulin concentrations by approximately 80%, as a result of ketoconazole-induced inhibition of CYP3A4. However, because of the low systemic exposure to retapamulin after topical application, this increase does not appear pose a significant risk for systemic toxicity. At this time, no dosage adjustment for retapamulin is recommended for

patients receiving ketoconazole. There have been no other reports of drug-drug interactions with retapamulin.[1,2]

Adverse Effects

The most common adverse effect associated with retapamulin administration in children enrolled in clinical trials was application site irritation (in 1.9% of patients). Other adverse effects, reported in similar rates in both retapamulin and control subjects, included application site pruritus (1.9%), diarrhea (1.7%), nasopharyngitis (1.5%), headache (1.2%), pyrexia (1.2%), and eczema (1%). In adults who received retapamulin during clinical trials, headache was the most frequently reported adverse effect, occurring in 2% of patients. The overall adverse effect profile in adults has been similar to that observed in children.[1,2]

Dosing Recommendations

A thin layer of retapamulin should be applied over the infected area twice daily for 5 days. The manufacturer recommends that no more than 2% of the patient's total body surface area be treated at one time. The area may be covered by a sterile bandage or gauze if desired, but should not be covered with an occlusive dressing. Mucosal application of retapamulin has not been studied, and the ointment should not be applied intraorally, intranasally, intravaginally, or into the eye. Patients or caregivers should wash their hands after applying retapamulin to avoid accidental transfer to the eyes or mouth. [1,2]

Availability and Cost

Retapamulin (Altabax®; GlaxoSmithKline) is available as a 1% ointment in 5, 10, or 15 gram tubes. The average price ranges from $45 for the 5 gram tube to $130 for the 15 gram tube. GlaxoSmithKline's Bridges to Access program provides assistance with obtaining Altabax® for uninsured families. More information about the program is available on the company's website at www.bridgestoaccess.com. For comparison, a 22 gram tube of generic mupirocin 2% ointment has an average retail price of $44.[12]

Summary

Retapamulin offers an effective alternative to mupirocin for the topical treatment of impetigo in children. The ease of use, with twice daily dosing for 5 days, as well as its broad spectrum of activity and mild adverse effect profile, make it an attractive choice; however, the limited amount of clinical research available in the medical literature and the potential for development of resistant strains should be considered when evaluating the role of retapamulin in clinical practice.

References

1. Retapamulin. *Drug Facts and Comparisons*. Efacts [online]. 2007. Available from Wolters Kluwer Health, Inc. (accessed 7/22/07).
2. Altabax® prescribing information. GlaxoSmithKline, April 2007.
3. Rittenhouse S, Biswas S, Broskey J, et al. Selection of retapamulin, a novel pleuromutilin for topical use. Antimicrob Agents Chemother 2006;50:3882-5.
4. Gentry DR, Rittenhouse SF, McCloskey L, et al. Stepwise exposure of *Staphylococcus aureus* to pleuromutilins is associated with stepwise acquisition of mutations in *rplC* and minimally affects susceptibility to retapamulin. Antimicrob Agents Chemother 2007;51:2048-52.
5. Yan K, Madden L, Choudhry AE, et al. Biochemical characterization of the interactions of the novel pleuromutilin derivative retapamulin with bacterial ribosomes. Antimicrob Agents Chemother 2006;50:3875-81.
6. Pankuch GA, Lin G, Hoellman DB, et al. Activity of retapamulin against *Streptococcus pyogenes* and *Staphylococcus aureus* evaluated by agar dilution, microdilution, E-test, and disk diffusion methodologies. Antimicrob Agents Chemother 2006;50:1727-30.
7. Goldstein EJC, Citron DM, Merriam CV, et al. Comparative in vitro activities of retapamulin (SB-275833) against 141 clinical isolates of *Propionibacterium* spp., including 117 *P. acnes* isolates. Antimicrob Agents Chemother 2006;50:379-81.
8. Odou MF, Muller C, Calvet L et al. In vitro activity against anaerobes of retapamulin, a new topical antibiotic for treatment of skin infections. J Antimicrob Chemother 2007;59:646-51.
9. Orange A, van der Wouden J, Konig S, et al. Retapamulin ointment for the treatment of impetigo in adults and children: results of a phase III, placebo-controlled, double-blind trial [abstract]. J Am Acad Dermatol 2007;56(suppl 2);Ab4.
10. Free A, Roth E, Dalessandro M, et al. Retapamulin ointment twice daily for 5 days vs oral cephalexin twice daily for 10 days for empiric treatment of secondarily infected traumatic lesions of the skin. Skinmed 2006;5:224-32.
11. Parish LC, Jorizzo JL, Breton JJ, et al. Topical retapamulin ointment (1% wt/wt) twice daily for 5 days versus oral cephalexin twice daily for 10 days in the treatment of secondarily infected dermatitis: results of a randomized controlled trial. J Am Acad Dermatol 2006;55:1003-13.
12. 2007 Drug Topics Red Book. Montvale, NJ: Thompson Healthcare, 2007.

Pharmacology Literature Review

Infliximab Review

This extensive review focuses on the use of infliximab, a monoclonal antibody to tumor necrosis factor alpha (TNFα), in the treatment of children and adolescents with inflammatory bowel disease. The article begins with a general overview of the drug and its mechanism of action, then turns to studies supporting its use in both luminal and fistulizing Crohn's disease. The authors include a discussion of the studies which were used by the FDA to support a pediatric indication for infliximab. The article also includes a section on the use of infliximab in ulcerative colitis and a review of its adverse effect profile. Veres G, Baldassano RN, Mamula P. Infliximab therapy in children and adolescents

with inflammatory bowel disease. **Drugs 2007;67:1703-23.**

Intrapleural Doxycycline for Pleural Effusions

A sequential sample of 12 children treated with intrapleural doxycycline for postcardiotomy pleural effusions is described in this brief report. The patients ranged in age from 2 weeks to 2.5 years and were treated for effusions lasting at least 7 days. Eighteen 18 courses of doxycycline were administered, using an average dose of 19 mg/kg per course. The doses were diluted to 2-8 mg/mL and injected through a chest tube. The dose was allowed to remain in place for 6 hours before being drained. The treatment success rate (defined as no further drainage) was 94%. The mean time from dosing to chest tube removal was 130 hours, with a wide range from 8-453 hours. Chest pain was the most common adverse effect reported. The authors concluded, based on this small sample, that intrapleural doxycycline may be a useful tool in the management of persistent pleural effusions after cardiac surgery. Hoff DS, Gremmels DB, Hall KM, et al. Dosage and effectiveness of intrapleural doxycycline for pediatric postcardiotomy pleural effusions. **Pharmacotherapy 2007;27:995-1000.**

Medication Use During Lactation

This article compares the recommendations of 10 different sources for information on medication use during lactation. The sources included common reference texts, such as the *Physician's Desk Reference*, and specific references such as *Drugs in Pregnancy and Lactation* and *Medications and Mother's Milk*, as well as free and subscription on-line databases and the databases used by two large retail pharmacies. Fourteen drugs that might be used by breastfeeding women were evaluated, including anti-infectives, antihypertensives, methotrexate, pantoprazole, and two selective serotonin reuptake inhibitors. The authors found significant variation among the recommendations in the sources they evaluated. Many of the sources did not include recent research and several advised against breast-feeding during treatment, even when there were data suggesting the medication was safe. Akus M, Bartick M. Lactation safety recommendations and reliability compared in 10 medication resources. **Ann Pharmacother 2007;41:1352-60.**

Topical Calcineurin Inhibitor Review

The authors of this review focus on the safety of the topical calcineurin inhibitors, tacrolimus and pimecrolimus, in children and adults. They discuss the potential for systemic immunosuppression and carcinogenic effects with chronic use. The decision by the FDA to add a black box warning to the labeling of both drugs regarding their potential association with malignancies is also addressed. The authors concluded from their review that there are no data to support a link between the topical calcineurin inhibitors and an increase in malignancy, but urge prescribers to use these agents within the recommended dosing guidelines. Munzenberger PJ, Montejo JM. Safety of topical calcineurin inhibitors for the treatment of atopic dermatitis. **Pharmacotherapy 2007;27:1020-8.**

Treatments for Adolescent Obesity

While the therapeutic options for obesity are limited, there has been growing interest in using the available agents in the adolescent population. This new review incorporates studies on orlistat, a lipase inhibitor recently approved by the FDA for use in adolescents, as well as sibutramine, a norepinephrine and serotonin reuptake inhibitor, and metformin, an oral biguanide used in type 2 diabetes. In addition to an overview of study results, the authors present their guidelines for obesity management. Dunican KC, Desilets AR, Montalbano JK. Pharmacotherapeutic options for overweight adolescents. **Ann Pharmacother 2007;41:1445-55.**

Formulary Update

The Pharmacy and Therapeutics Committee did not meet in August. Meetings will resume next month.

Contributing Editor:Marcia L. Buck, Pharm.D.
Editorial Board: Kristi N. Hofer, Pharm.D.
Michelle W. McCarthy, Pharm.D.
If you have comments or suggestions for future issues, please contact us at Box 800674, UVA Health System, Charlottesville, VA 22908 or by e-mail to mlb3u@virginia.edu. This newsletter is also available at www.healthsystem.virginia.edu/internet/pediatrics/pharma-news/home.cfm