



Retapamulin: New Topical Antibacterial

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Introduction

Retapamulin is a novel, semi synthetic, topical agent in a new class of antibacterial drugs known as Pleuromutilins (Pleurotus mutilus an edible mushroom). It was approved by the US FDA for the topical treatment of impetigo, in April 2007, and approved in Europe for the treatment of impetigo and infected small lacerations, abrasions or sutured wounds in June 2007(1,2).

Skin infections are major burden of patients attending dermatological OPD. The most common bacteria associated with uncomplicated superficial skin and soft tissue infections (SSTI) include the gram-positive organisms *Staphylococcus aureus* (55.2%), beta-hemolytic *Streptococci* (5.0%), and Coagulase negative *Staphylococci* (4.9%) (3,4). Treatment of these infections has been compromised by (a) development of resistance in *S. aureus* to beta-lactams ('methicillin' resistance), fluoroquinolones, macrolides, clindamycin, fusidic acid, and mupirocin (b) poor intrinsic activity on *S. pyogenes* of other topical antimicrobial drugs, such as neomycin and bacitracin (5,6). This stimulated a search for new topical antibacterial agents with the appropriate balance of drug developability, microbiological attributes and low propensity for inducing bacterial resistance. Retapamulin was the first agent approved for human use in the pleuromutilin class of antibacterials.

MOA

In common with macrolides, tetracyclines and aminoglycosides, retapamulin inhibits bacterial protein synthesis, but binds domain V of 23s rRNA on ribosomal subunit 50S thus inhibiting ribosomal peptidyl transferase activity. Additionally it partially inhibits the binding of the initiator tRNA substrate to the ribosomal P-site (5,7).

Antimicrobial Spectrum

Retapamulin shows very good in vitro activity against most of the facultative aerobic organisms involved in skin & soft tissue infections: methicillin susceptible as well as resistant *S.aureus*, coagulase negative staphylococcus, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococci viridans*, *H. influenza*, *Moraxella catarrhalis*,

corynebacterium spp & *Micrococcus* spp (8). It is a bacteriostatic drug, but bactericidal at high concentration. The minimum bactericidal concentration (MBC) is 1000 times higher than the minimum inhibitory concentration (MIC). The MIC against *S. aureus* is between 0.03 and 0.25 mcg/ml and for *S. pyogenes* it is between 0.008 and 0.03 mcg/ml. It has substantial post antibiotic effect (PAE) against *S. aureus* and *S. pyogenes*, which may contribute to the efficacy observed after twice daily application of 1% ointment for five day (4). It is as potent as Co-amoxiclav, imipenem, metronidazole and clindamycin against gram negative anaerobes *Prevotella* spp, *Porphyromonas* spp and *Fusobacterium* spp. It is more active than clindamycin, metronidazole and ceftriaxone against anaerobic gram positive cocci. Its activity against *Propionibacterium* spp, largely associated with skin infections & especially *acne vulgaris*, has also been demonstrated. Most importantly, it maintains its activity against organisms that are resistant to a number of antimicrobials including methicillin, erythromycin, fusidic acid, mupirocin, azithromycin and levofloxacin (4,8).

Pharmacokinetics

Systemic exposure following Retapamulin topical application to intact or abraded skin is minimal. It is 94% protein bound and metabolized in liver by CYP3A4 enzyme via monooxygenation and N-demethylation methods to numerous metabolites.

Clinical Uses

Retapamulin offers a novel, effective, and convenient topical treatment for skin infections like impetigo, folliculitis, furuncle, carbuncle, infected dermatoses (atopic dermatitis, atopic contact dermatitis, psoriasis), infected sutured wounds and traumatic lesions (small lacerations, cuts, abrasions). In clinical trials in patients with impetigo, topical retapamulin 1% ointment twice daily for 5 days (the approved regimen) was as effective as topical fusidic acid. In patients with secondarily infected traumatic lesions, treatment with retapamulin was equivocal to that with 10 days oral cefalexin (2,9).

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Side effects

The most common adverse effect at application site is irritation, sometimes burning, redness, pruritus, eczema and oozing may be seen. Headache, pyrexia, diarrhoea and nausea are rare. Retapamulin is classified as pregnancy category B; however, there have been no adequate human studies in this population group. The safe use of retapamulin during breast-feeding has not been established (1,2).

Drug Interactions

Based on in vitro P450 inhibition studies and the low systemic exposure observed following topical application of retapamulin, it is unlikely to affect the metabolism of other P450 substrates such as ketoconazole. So, drug interactions are minimal (1,2).

Dosage and Administration

A thin layer of retapamulin should be applied to the affected area up to 100 cm² in total area in adults or 2% total body surface area in pediatric patients aged 9 months or older) twice daily for five days. The treated area may be covered with a sterile bandage or gauze dressing if desired (1,2).

Antimicrobial Resistance

Multiple-step and single-step studies suggest that retapamulin has a low potential to select for resistant mutants in *S. pyogenes* and *S. aureus*. Study done by Gentry DR, on *S. aureus* suggested that stepwise reduction in pleuromutilin susceptibility occurring concurrently with stepwise acquisition of mutations in *rplC*. A novel multidrug resistance phenotype mediated by the Cfr rRNA methyltransferase on nucleotide A2503 of 23S rRNA is observed in *Staphylococcus aureus*. This cause a potential clinical threat of cross-resistance in the antibiotics that targets the ribosomal peptidyl transferase center (PTC) like phenicols, lincosamides, oxazolidinones, pleuromutilins, and streptogramin antibiotics (10-12).

Conclusion

Given the novel mode of action, low potential for cross-resistance with established antibacterial agents and high in vitro potency against many bacterial pathogens commonly recovered from SSSIs, retapamulin is a valuable enhancement over existing therapeutic options. It could be valuable therapeutic tool for uncomplicated SSSIs. Research is on and is proposed that new antibacterial agents might be developed from pleuromutilin derivatives in the future.

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