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INTRODUCTION

Skin infections are a common reason for patients to seek attention from dermatologists. The most common bacteria found in skin and soft tissue infections (SSTI) include the gram-positive organisms *Staphylococcus aureus* (55.2%), β -hemolytic *Streptococci* (5.0%), and *Coagulase-negative Staphylococci* (4.9%). Most of these bacteria causing SSTI have become resistant to the leading topical antimicrobials used in clinical practice. Antibiotics with a novel mechanism of action are needed to address the rising resistance to established classes of both systemic and topical agents. Resistance has already developed to two of the most commonly used topical antibiotics, fusidic acid and mupirocin.^[1] Retapamulin, a novel topical antibacterial agent, will probably replace the use of mupirocin and fusidic acid.^[2] It was approved by FDA, in 2007, for topical treatment of impetigo.^[3] European Medicines Agency approved this drug also for infected wounds caused by *S. pyogenes* and methicillin susceptible *S. aureus*.^[4]

Synthesis

Retapamulin is a derivative of the naturally occurring pleuromutilin, produced by *Pleurotus mutilins* (now called *Clitopilus scyphoides*), an edible mushroom.^[5] Pleuromutilin was discovered in 1951, but it was not until the early 1970s that its potential for use as an antimicrobial was more fully recognized. Other agents in this class (tiamulin and valnemulin) have been developed as veterinary antibiotics. These drugs have a common tricyclic mutilin core, a C21 keto group, essential for antimicrobial activity and various substituents at its C14, most of which are extensions of diverse chemical nature. Retapamulin is a C14-sulfanyl-acetate derivative of pleuromutilin [Figure 1].

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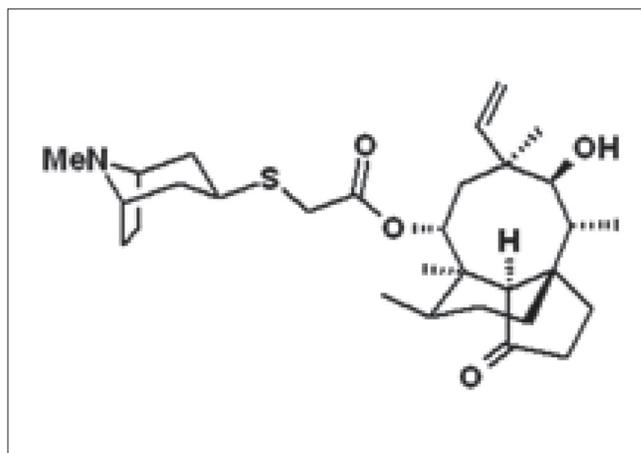


Figure 1: Chemical structure of retapamulin {mutilin 14-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-sulfanyl-acetate}^[6]

MECHANISM OF ACTION

The pleuromutilin class has a unique mode of action which involves inhibition of bacterial protein synthesis at the level of bacterial 50s ribosome.^[1] It binds to domain V of 23s rRNA, inhibits ribosomal peptidyl transferase activity and partially inhibits the binding of the initiator tRNA substrate to the ribosomal P-site.^[7] The ribosomal binding site for pleuromutilin overlaps with that for chloramphenicol and puromycin, hence both drugs compete with retapamulin for the binding site.^[8]

Antimicrobial spectrum

Retapamulin is effective against gram-positive and some gram-negative organisms. It includes *Streptococcus pyogenes*, *Streptococcus agalactiae*, β -hemolytic streptococci, *Streptococci viridans*, *Staphylococcus aureus*, *Coagulase-negative staphylococci*, *Propionibacterium* spp (including *P. acnes*), *Prevotella* spp, *Porphyromonas* spp, *Fusobacterium* spp, *Bacteroides* and *Clostridium*.

It is a bacteriostatic drug, but may be 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

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for *S. pyogenes* it is between 0.008 and 0.03 mcg/ml.^[9] 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.^[10]

However, retapamulin showed minimal or no activity against enterococci and gram-negative bacilli. It is active against *B. fragilis* but less active against other members of the *B. fragilis* group, especially *B. thetaiotaomicron*.

It is as potent as Co-amoxiclav, imipenem, metronidazole and clindamycin against *Prevotella* spp, *Porphyromonas* spp and *Fusobacterium* spp. It is also more active than clindamycin, metronidazole and ceftriaxone against anaerobic gram- positive cocci.^[11]

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.

Pharmacokinetics

Bioavailability is low. Hence systemic exposure is minimal following topical application to intact or abraded skin. It is 94% protein bound and metabolized in liver by monooxygenation and N-demethylation to numerous metabolites. The main enzyme responsible for metabolism in liver microsome is CYP3A4.

Side effects

The most common adverse effect is pruritus at the application site.^[12] Others are blisters, burning, redness, swelling, headache, diarrhea, eczema and oozing at the site where the ointment is applied. Retapamulin is classified as pregnancy category B; however, there have been no adequate human studies in this population group.

Drug resistance

Retapamulin has demonstrated excellent activity *in vitro* against *S. aureus*, irrespective of their level of resistance to other antimicrobials.^[13] One study has shown that bacterial resistance *in vitro* is through two mechanisms: Mutation in protein L3 close to the peptidyl transferase center and the development of drug efflux mechanisms.^[14] Mutation in L3 is a multi-step process which appears to be slow to emerge. Evidences from multiple-step and single-step studies also suggest that retapamulin has a low potential to select for resistant mutants in *S. pyogenes*

and *S. aureus*. Retapamulin had the lowest rate of spontaneous mutations by single step passaging and the lowest parent and selected mutant MICs by multi step passaging among all drugs tested for all *S. aureus* strains and three *S. pyogenes* strains which yielded resistant clones.^[15] Another study showed a stepwise reduction in pleuromutilin susceptibility occurring concurrently with stepwise acquisition of mutations in *rplC*.^[16] A potential clinical threat of cross-resistance in the antibiotics that targets the ribosomal peptidyl transferase center (PTC) is the multidrug resistance phenotype mediated by the *cfr* rRNA methyltransferase. This gene encodes a methyltransferase that modifies the PTC nucleotide A2503, and is responsible for resistance to phenicols, lincosamides, oxazolidinones, pleuromutilins, and streptogramin antibiotics.^[17]

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 nine months or older) twice daily for five days. The treated area may be covered with a sterile bandage or gauze dressing if desired.

Drug interactions

Drug interactions are less due to low systemic exposure following topical application. Dosage adjustments are unnecessary when co-administered with CYP3A4 inhibitors such as ketoconazole.

Indications

It is used in adults and children over nine months of age for topical treatment of impetigo and infected wounds caused by *S. pyogenes* and methicillin susceptible *S. aureus* (MSSA).^[3,4]

CONCLUSIONS

Retapamulin, a novel pleuromutilin derivative, could probably provide a valuable therapeutic option for the management of skin and soft tissue infections caused by *S. pyogenes* and *S. aureus* resistant to the most commonly used topical antibiotics.

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