DRUG REVIEW

Retapamulin: New Topical Antibacterial

Cheena Langer, Vivek Mahajan*, Vipin Gupta

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, diarrohea 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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Retapamulin is a topical antibiotic developed by GlaxoSmithKline. It is the first drug in the new class of pleuromutilin antibiotics to be approved for human use. It is marketed as an ointment under the brand names Altabax and Altargo.Â Retapamulin is an antibacterial agent, specifically a protein synthesis inhibitor. The medication selectively inhibits bacterial protein synthesis by interacting at a site on the 50S subunit of the bacterial ribosome through an interaction that differs from other antibiotics.[2]. Pharmacokinetics. Systemic exposure following topical application through intact skin is low.[2]. Contraindications. None yet reported.[2]. Retapamulin is a new topical pleuromutilin antibiotic for the treatment of skin and skin-structure infections, including impetigo. In vitro studies indicate that retapamulin has a unique mode of action that minimizes the potential for target-specific cross-resistance with other antibacterials and a limited potential for resistance development. Retapamulin is a topical antibiotic developed by GlaxoSmithKline. It is the first drug in the new class of pleuromutilin antibiotics to be approved for human use. It is marketed as an ointment under the brand names Altabax and Altargo. Retapamulin was approved by the United States Food and Drug Administration in April 2007 for the treatment of bacterial skin infections such as impetigo.Â Retapamulin is an antibacterial agent, specifically a protein synthesis inhibitor. The medication selectively inhibits bacterial protein synthesis by interacting at a site on the 50S subunit of the bacterial ribosome through an interaction that differs from other antibiotics.[2]. Pharmakinetics. Systemic exposure following topical application through intact skin is low.[2]. Contraindications. None yet reported.[2]. Retapamulin is the first agent in the new pleuromutilin class of antibacterials to become commercially available for clinical use in humans. Retapamulin acts as a potent inhibitor of bacterial protein synthesis and has a unique mode of antibiotic action.Â Clinical pharmacology studies showed low systemic exposure with topical use of retapamulin, and a favorable tolerability profile. In clinical efficacy trials involving pediatric and adult patients who received retapamulin twice daily for five days, retapamulin was highly effective in the treatment of impetigo, secondarily infected traumatic lesions and secondarily infected dermatitis. Further, the clinical efficacy and safety profile of retapamulin was comparable to that of commonly used oral and topical antibiotics. Retapamulin: New Topical Antibacterial. Cheena Langer, Vivek Mahajan*, Vipin Gupta. 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.