REVIEW ARTICLE

A Comprehensive Review on Ozenoxacin Cream for Treatment of Impetigo

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ABSTRACT

A frequent bacterial skin infection in youngsters is impetigo. In contrast to other quinolones like levofloxacin, nadifloxacin, and ofloxacin, ozenoxacin exhibits lower minimum inhibitory concentrations and better antibacterial activity. Because of its limited systemic absorption and lack of known drug interactions, ozenoxacin is notable for not activating cytochrome P450 enzymes in vitro. Despite being a relatively new antibacterial agent, ozenoxacin has been used in clinical settings. To shed light on its efficacy in patients, a meta-analysis has not yet been completed. The purpose of this meta-analysis and systematic review is to assess the effectiveness of ozenoxacin in treating impetigo, specifically when applied as a 1% topical cream.

Keywords: Ozenoxacin, Quinolone, Impetigo, Topical cream, Antibiotics

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INTRODUCTION

Impetigo is treated with ozenoxacin, a unique synthetic quinolone antibiotic. Impetigo can be treated with an approved topical cream containing 1 percent.[1] Ozenoxacin demonstrates efficacy against certain bacterial strains that have acquired resistance to fluoroquinolone antibiotics.[2] With a molecular weight of and a chemical formula of $C_{21}H_{21}N_3O_3$, ozenoxacin is a white, crystalline powder. Quinolones represent a significant category of antibacterial agents that are widely utilized in both inpatient and outpatient environments for treating a variety of human bacterial infections caused by both Gram-positive and Gram-negative bacteria. These pharmaceuticals are frequently utilized in the management of sexually transmitted infections, infection of the respiratory system, infection of the urinary system, infection of the intra-abdomen, infection of the skin and soft tissues, and infection of the bones and joints.[3] In a set of carefully designed phase I trials with healthy adults, researchers explored the effects of ozenoxacin applied topically beneath protective dressings. With minimal to no indications of cumulative irritation, phototoxicity, photoallergy, or any chance of sensitisation, the results were encouraging. Moreover, they have been employed in urologic surgery, as a prophylactic measure in cancer patients who are neutropenic and vulnerable to spontaneous bacterial peritonitis in cirrhosis patients. Adults and children older than two months are prescribed ozenoxacin, a topical, non-fluoridated quinolone antibiotic, to treat either bullous or non-bullous impetigo. Ozenoxacin demonstrates irreversible binding to both DNA gyrase and topoisomerase IV play a crucial role in preventing DNA replication. Quinolone antibiotics similarly target these enzymes, which are crucial for various nucleic acid processes in bacteria.[4,5] Additionally, they are essential in controlling the degree of DNA under- and over-winding, in addition to facilitating the untangling and resolution of knots in bacterial chromosomes. Quinolone antibiotics exhibit differential inhibitory effects on these enzymes. These enzymes play a vital role in various biological processes, such as the de-catenation of the two newly synthesized DNA strands and the alleviation of superhelical tension that accumulates prior to the action of polymerases.[6] They thus have a vital function in the transcription and replication of bacterial DNA. Our youngest children are frequently affected by impetigo, a common bacterial skin infection, particularly those under five years old. This pesky infection is widespread across the globe, especially among children in low and low-middle-income nations, as well as in underprivileged neighborhoods of wealthier countries. In the general population, the median prevalence of impetigo is 11.2 percent; In children, the prevalence is 12.3%, which is 2.5 times greater than the 4.9% observed in adults.[7,8] Impetigo lesions are predominantly found on the hands, neck, and face; however, pruritic lesions have the potential to allow the infection to spread to nearby areas and other body parts. The main culprits behind impetigo are the notorious bacteria *Staphylococcus aureus* and *Streptococcus pyogenes*. These two troublemakers are linked to the nonbullous type of the infection, making up about 70% of all cases.[9] Staphylococcus aureus is the sole troublemaker behind impetigo, thanks to its ability to churn out toxins that slough off skin. This pesky pathogen is particularly worrisome in places like schools and daycare centers, where its highly contagious nature can spread like wildfire.[10,11] To mitigate the transmission of infection, it is advisable for children to remain at home for a period of twenty-four hours following the initiation of suitable antibiotic therapy. Controlling the disease is also essential to lessen scarring from

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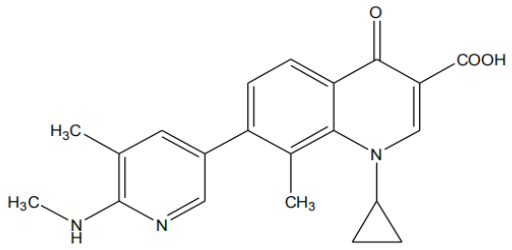

Figure 1: Ozenoxacin Structure

scratches, relieve symptoms (itching, sores), and prevent uncommon but harmful outcomes like glomerulonephritis or rheumatic heart disease. When impetigo is treated with antibiotics, the likelihood of transmission from person to person can be considerably reduced, leading to a swift alleviation of symptoms.

According to clinical practice guidelines, when patients present with widespread lesions that don't improve with topical treatments, it's advisable to consider prescribing antibiotics. This approach is particularly important for tackling systemic infections and managing outbreaks that affect multiple individuals. Topical anti-microbial medications are recommended for impetigo that is localized. By directly applying a high dosage of medication to skin infections, topical antibacterial therapy increases the antimicrobial's capacity to overcome bacterial resistance. Additionally, because topical medications absorb very little, they generally avoid the detrimental systemic effects of oral medications.[12,13] Topical antibiotics, once the stalwarts of clinical treatment, are now facing a formidable foe in the form of resistant Gram-positive bacteria, particularly the notorious *Staphylococcus aureus*. The rise of *Staphylococcus aureus* that is resistant to methicillin (MRSA) has become a pressing global concern in the battle against antibiotic resistance. These hardy strains have only proliferated due to the increase in community-acquired MRSA infections. Alarmingly, reports from various countries indicate that Staphylococcus aureus is developing resistance to fusidic acid, jeopardizing the effectiveness of this medication. Moreover, the widely used topical antibiotic mupirocin is also encountering resistance, with a recent extensive study revealing that a staggering 31.3 percent of *Staphylococcus aureus* isolates (n = 358) from soft tissue and skin infections, mostly in children, have developed resistance to this therapy.[14,15] Patients diagnosed with empirically treated conditions, such as impetigo, ought to be aware of the rising prevalence of antibiotic resistance. In these situations, treatment approaches often proceed without the valuable insights that microbial cultures and susceptibility tests could provide, leaving healthcare providers to navigate management strategies in the dark. It goes without saying that more recent antimicrobial drugs that target resistant isolates and function differently from the ones currently used to treat impetigo are desirable. This review examines the innovative non-fluorinated topical quinolone known as ozenoxacin, its pharmacokinetic and microbiological properties, and recent studies showing its efficacy in treating impetigo. When compared to other quinolone antibiotics, including ofloxacin, nadifloxacin, and levofloxacin, zeobactin demonstrates enhanced antibacterial efficacy and lower minimum inhibitory concentrations. Conversely, ozenoxacin exhibits limited systemic absorption and its potential drug interactions remain unidentified; Additionally, it doesn't trigger the activity of cytochrome P450 enzymes in laboratory settings. Despite being a relatively recent addition to the class of antibacterial agents, ozenoxacin has already been implemented in clinical practice.[16] This systematic review and meta-analysis aimed to assess how effective ozenoxacin is in treating impetigo in patients, particularly when using a 1% topical cream. However, no comprehensive analysis was conducted to assess its effectiveness.

Categories for Quinolones

The quinolone class of antibiotics has been divided into several categories. Chemical structure serves as the foundation for chemical classification. The quinolones are categorized into four groups: mono-, bi-, tri-, and tetracyclic.[17] Each of these categories can be sliced and diced even further based on whether a four atom makes an appearance at position 6 or not. The primary quinolone indications of use are listed in the table 1 along with their biological classification.

Structure

Ozenoxacin, a groundbreaking member of the quinolone family, boasts the International Union of Pure and Applied Chemistry (IUPAC) name of 1-cyclopropyl [8-methyl {7, 5-methyl, 6-methyl-amino-pyridin, 3yl, 4-oxo-quinoline quinoline -3- carboxylic acid}. With a molecular formula of $C_{21}H_{21}N_3O_3$, this innovative antimicrobial agent stands out as the first nonfluorinated quinolone. Its unique structure (Figure 1) features a pyridinyl group nestled at the C_7 position, showcasing intriguing structural parallels with quinoline.

Mechanism of action

Quinolones unleash their antimicrobial prowess by putting the brakes on two key players in the bacterial world: DNA gyrase and type II topoisomerase, particularly topoisomerase IV. These enzymes are the unsung heroes of bacterial DNA synthesis. DNA gyrase is like a master craftsman, expertly creating negative supercoils in DNA, a crucial step for transcription, replication, and chromosome assembly. Meanwhile, topoisomerase IV steps in to untangle the DNA strands after they've been replicated, ensuring everything is in order. Both of these enzymes boast a tetrameric structure, with DNA gyrase made up of two A subunits, courtesy of the gyrA gene, and two B subunits, thanks to the gyrB gene. Together, they form a dynamic duo essential for bacterial life.[18,19] Furthermore, topoisomerase IV is composed of two A sub-units (par C or grl A; the latter is produced by the par C or grl A genes in *Staphylococcus aureus*) and two B subunits (par E or grl B; the latter is expressed by the par E or grl B genes in S. aureus). Inhibiting topoisomerase IV is one of the quinolones' advantages over DNA gyrase. Examples of these include levofloxacin, sparfloxacin, nadifloxacin,

Table 1: Quinolones' biological categorization and primary uses

Classification/ Generation	Quinolones	Antimicrobial spectrum	Administration	Indications
First	Cinoxacin Lomefloxacin Nalidixic acid Pipemidic acid	Effective on Gram -ve bacteria such as E. Coli, Salmonella, proteus, Shigella etc but not pseudomonas species.	Oral Route	Non complicated UTI
Second	Enoxacin Nadifloxacin Ciprofloxacin Ofloxacin	The pioneering quinolones pack a punch against a variety of foes, including mycobacteria, those quirky atypical pathogens, the notorious *Pseudomonas aeruginosa*, and the infamous *Neisseria gonorrhoeae*. They also take on the formidable *Staphylococcus aureus* and its less menacing cousin, *Staphylococcus epidermidis*, as well as the pesky *Haemophilus influenzae* and *Moraxella catarrhalis*.	Oral, Parenteral, topical	Infections of the skin and soft tissues, STIs, and prostate inflammation.
Third	Pazufloxacin Levofloxacin Grepafloxacin Balofloxacin	Just like the advancements seen in second-generation drugs, there's a notable boost in their ability to tackle atypical infections, combined with a broader spectrum of activity against bacteria that are gram-positive. This includes both the penicillin-sensitive and the more resilient penicillin-resistant strains of Streptococcus pneumoniae.	Oral, Parenteral	Flare-ups of respiratory infections can sometimes be linked to a variety of culprits, including sexually transmitted infections (STIs), gastroenteritis, osteomyelitis, and pneumonia picked up in the community.
FOURTH	Clinafloxacin Trovafloxacin Prulifloxacin Moxifloxacin	Having broad coverage against anaerobic bacteria, these agents are comparable to those of the third generation.	Oral, Parenteral	Apart from pyelonephritis and complex UTIs, this observation applies equally to first, second, and third-generation agents.
OTHERS	Ozenoxacin Delafloxacin Zabofloxacin	Exhibiting enhanced efficacy against anaerobic, Gram-positive, and atypical bacteria, this agent demonstrates a potency that is comparable to that of fourth-generation alternatives.	Oral, Parenteral, Topical	Infections of the respiratory system and dermatological infections.

and ciprofloxacin. Ozenoxacin works its magic by locking onto DNA gyrase or topoisomerase IV, halting DNA replication in its tracks with its powerful dual inhibition. The drug is bactericidal because of the rapid cell death that typically ensues.

Pharmacokinetics

When the skin is either intact or abraded, the absorption of ozenoxacin into the systemic circulation is minimal. The stratum corneum exhibits the highest concentrations of drugs, succeeded by the epidermis and the dermis, while the concentrations in the stratum corneum are below the quantification threshold. Nutrient absorption is identical in the skin types of adults and children. Because of the low systemic absorption, in-vivo research on human tissue distribution, metabolism, and elimination has not been conducted.[20,21] Studies conducted in vitro have demonstrated that the average protein binding of ozenoxacin in human plasma samples is relatively low

(between 85 and 87 percent) and is not influenced by concentration. It has been found that in both freshly generated human skin discs and human hepatocytes grown in vitro, ozenoxacin is metabolically stable.

Antimicrobial Spectrum

Quinolones pack a powerful punch when it comes to battling bacteria, They demonstrated their ability to kill both gram-positive and gram-negative bacteria. Their antibacterial might spans a diverse array of pathogens. Notably, several gram-positive culprits, such as *Streptococcus pyogenes*, *Propionibacterium acnes*, and the infamous *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE) methicillin-resistant, find themselves vulnerable to the formidable effects of ozenoxacin, even those resistant strains of *Staphylococcus aureus* and *Staphylococcus epidermidis* that have evaded other treatments. When stacked against its quinolone counterparts like ofloxacin, nadifloxacin, and levofloxacin, ozenoxacin shines with its superior antibacterial prowess and impressively lower minimum inhibitory concentration (MIC).[22,23] Research indicates that ozenoxacin facilitates a more rapid microbiological clearance, while also demonstrating comparable overall clinical efficacy at the conclusion of treatment. In preclinical animal studies, ozenoxacin has exhibited a faster rate of microbiological clearance in comparison to fusidic acid and mupirocin; however, corresponding clinical trials in humans are currently insufficient. Furthermore, the minimum inhibitory concentration (MIC) of ozenoxacin is notably lower than that of retapamulin, mupirocin, and fusidic acid.[24] In the context of in vivo studies involving *Streptococcus galactiae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*, the medication demonstrates significant antibacterial efficacy and rapid penetration into bacterial cells during the initial minute of contact, distinguishing it from other quinolone antibiotics.[25-28]

Indications

The suggested therapeutic approach for impetigo resulting from *Staphylococcus aureus* and *Streptococcus pyogenes* involves the use of topical ozenoxacin. This medication is designed to tackle both bullous and nonbullous impetigo in both adults and infants under two months of age in the United States and Canada. Moreover, it has received the green light for topical use in those six months and older, specifically for nonbullous impetigo, across twelve countries in the European Union.[29]

Composition and Storage

The 10 gram vials of ozenoxacin with 1% cream (10 mg/g) are available. This enchanting crystalline powder dances between shades of white and soft yellow, often gracing the shelves as a delicate pale yellow cream. To keep its magic intact, store the tube at room temperature and make sure to use it within 45 days of cracking it open. The potion is crafted with a blend of ingredients, including benzoic acid (E 210), filtered water, stearyl alcohol, oleoyl macrogol glycerides, propylene glycol, ethylene glycol monopalmitostearate, Octyldodecanol, and a sprinkle of polyethylene glycol-6 and 32 stearates, all coming together to create a truly remarkable formulation.

Dosage and Administration

Those who require it should apply a thin layer of ozenoxacin cream twice daily for five days to the affected area. This remedy is suitable for anyone aged 12 and older, with a maximum treatment zone of 100 cm^2. Youngsters under 12 can also have up to 100 cm^2 treated, or 2% of their total body surface area. If desired, the area can be covered with clean gauze or bandages. Should there be no noticeable improvement within three days of starting the treatment, a reassessment is essential, and other treatment options should be explored.[30,31]

Adverse Effects and Safety Profile

With no major negative side effects making headlines, ozenoxacin is seen as having a commendable safety record. However, there is just one recorded instance of preexisting rosacea and seborrhoeic dermatitis worsening together. Ozenoxacin 1% formulations passed dermal tolerability testing with minimal to no tendency to cause phototoxicity, photoallergy, sensitisation, or irritation. For individuals whose life expectancy is less than two months, the safety and efficacy of the medication remain uncertain. A dosage adjustment is not necessary for elderly individuals who do not have renal or hepatic impairment. There hasn't been any research done on expecting and breast feeding mothers.[32] Negative effects are not expected, though, because systemic absorption is so low. When taking ozenoxacin while breastfeeding, it is advised not to apply it to the breast region to avoid inadvertent drug absorption by the nursing infant. In young animals, quinolones may cause chondrotoxicity. Nevertheless, in rats administered oral ozenoxacin, there were no alterations in cartilage that were deemed significant from a toxicological or histopathological perspective. It is believed that ozenoxacin's lack of fluorination at the C–6 position enhances its safety profile in comparison to other quinolones. Children do not absorb chemicals systemically, which rules out the potential of chondrotoxicity.[33]

Drug Interactions

Ozenoxacin has been shown to not activate cytochrome P450 enzymes in vitro. Furthermore, due to its minimal systemic absorption, there are no identified drug interactions associated with its use. However, it is important to note that individuals with a known allergy to ozenoxacin or any of its components should avoid this medication, as well as newborns younger than two months old, are the only known contraindications as of now, because there is inadequate information regarding safety in that age range.[34]

CONCLUSION

Ozenoxacin is a brand-new topical antibiotic with consistent safety data, a positive microbiological profile, and quick clinical improvement. In vitro investigations have shown its effectiveness against resistant strains of Staphylococcus aureus, as well as against streptococci and staphylococci. It's critical to refrain from indiscriminate use and adhere to the antimicrobial stewardship rules in order to preserve the effectiveness of this advanced treatment. Ozenoxacin emerges as a promising treatment choice for tackling infections of the soft tissues and skin (STIs), which are prevalent in developing nations, owing to its established

safety profile and efficacy in addressing conditions such as impetigo. India, Europe, and the US have all approved this antibiotic. As a part of the quinolone class, ozenoxacin works by preventing DNA replication, which causes bacterial cells to die quickly. Studies on animals have shown that this class of antibiotics has higher intrabacterial concentrations and rapid penetration into bacterial cells, especially in the first few minutes after treatment. It boasts reduced minimum inhibitory concentrations (MICs) and a swifter microbiological clearance compared to its quinidine counterparts.

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