LOPROX (ciclopirox 0.77%): A novel approach to reducing the risk of lower extremity amputation among individuals with diabetes

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Abstract
Approximately 16 million Americans suffer from Type 1 and Type 2 diabetes, and almost 800,000 new cases are diagnosed each year[1]. Some 5-15% of these individuals will undergo lower extremity amputations during their lifetime[2]. The cost associated with diabetes related, lower extremity amputations in the United States approaches $2 billion, and these amputations have an estimated impact of 2,600 patient years of hospital stay annually[3]. The incidence of lower extremity amputations in diabetics can be significantly reduced if foot ulcerations and peripheral neuropathy are managed more effectively before the need for amputation[4]. Diabetic ulcerations from infections caused by fungal and bacterial pathogens can be managed using the broad spectrum, anti-fungal, anti-bacterial agent found in the hydroxypyridone LOPROX (ciclopirox 0.77%). Using LOPROX as both a treatment or a prophylaxis regimen for these pathogens could substantially reduce the number of lower extremity amputations, lower the amount spent annually on health care for diabetic patients, and decrease the morbidity associated with lower extremity amputations.

Introduction

Currently, type 1 and 2 diabetes affects nearly 16 million people[1] of which up to 15% will undergo lower extremity amputation during their lifetime[2]. Of all diabetes related amputations, approximately 80% are preceded by chronic foot ulcers[3,14,15] . This indicates that if the incidence of diabetes increases as expected over the next several years, there will be a continued rise in the incidence of lower extremity ulcers and amputations.

The impact of diabetes on Medicare is significant. Diabetes affects nearly 15% of the Medicare population, or approximately 6 million people over the age of 65[5]. The cost of care for Medicare patients is rising rapidly, in part, due to the large population of diabetics who rely on Medicare and the high cost of diabetes related complications including lower extremity ulcers and amputations. For instance, an average lifetime cost of lower extremity amputations was $48,152 in 1996 per individual while the expenditures for lower extremity ulcer patients were, on average, 3 times higher than those for Medicare patients in general: $15,309 vs. $5,226 [5]. This study showed that the aggregate Medicare spending for lower extremity ulcer-related patients (more than 400,000) was $1.45 billion[5]. Of that total, 73.7% went to inpatient hospitals, with the remaining amount to physicians, suppliers, outpatient hospitals, home health, SNF and hospice[5]. In a population of 10,000 individuals with diabetes, care for foot ulcerations to avoid amputations creates a 3-year savings ranging from $2,900-$4,442 per person with a history of foot ulcers[6]. Approximately 70% of the benefits would accrue in individuals 70 years of age or older[6]. Thus, the economic savings of measures to prevent development of diabetic ulcers, and, thus, amputations would be significant.

Patients who undergo a lower extremity amputation face not only significant economic loss but physical, social and emotional burdens as well. In individuals with diabetes

who have had one amputation, 30-50% require additional amputations within three years[2,7-9]. The death rate for individuals with a major amputation is 50% within 5 years of initial amputation[10,11]. The social and emotional impact of the loss of another limb or the loss of life has a major impact on the patient=s family as well as the patient.

Multiple studies show that one of the primary risk factors for lower extremity amputation is the presence of foot ulceration. Of all diabetes-related amputations, almost 80% are preceded by chronic foot ulcers[3,14,15]. Approximately 15% of all diabetic patients will develop a foot or leg ulceration at some time during the course of the disease, and 15-20% of these individuals will require a lower extremity amputation[1,2,13]. Ulceration of the foot is the leading cause of hospitalization for diabetes patients[2] whose infections are treated aggressively in an effort to avoid amputation.

Data show that more than 50 % of lower extremity amputations could be prevented by modifying risk factors utilizing better education among individuals with diabetes, improved treatment protocols and other prevention strategies[12,16] . Some of these strategies include improved control of diabetes through regulation of blood sugar levels, daily foot inspections, proper foot hygiene, prompt treatment of foot ulcerations and other preventative foot care which can result in a reduction in amputations and substantial economic savings for patients and managed care providers[6]. Unfortunately, many patients delay seeking treatment because of an inability to sense that a wound has developed due to peripheral neuropathy, common among diabetics. If an ulcer develops, immediate and effective treatment will reduce the number of chronic ulcerations, thus, reducing the number of lower extremity amputations. Research is still underway to improve prevention and treatment of diabetic ulcers and, thus, amputations.

Use of LOPROX (ciclopirox 0.77%) To Prevent and Treat Infection

Foot ulcers are cutaneous wounds that result from a combination of factors including disease, injury, neuropathy, vascular impairment and inefficient wound healing. Pathogens that cause ulcerations in diabetics include fungal and bacterial organisms, many of which are opportunistic in nature. Because of its anti-fungal, anti-bacterial, and anti-inflammatory properties[20-24], LOPROX (ciclopirox 0.77%) can be used to control these pathogens as a therapy that promotes rapid and complete healing, reducing the need for expensive surgical procedures. LOPROX (ciclopirox 0.77%) is currently indicated for topical treatment of a broad range of dermal fungal infections, including: tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum*, *T. mentagrophytes*, *Epidermophyton floccosum*, and *Microsporum canis*; candidiasis due to *Candida albicans*; and tinea versicolor due to *Malassezia furfur.*

In diabetic patients, there is a cascade of events that can lead to infection eventually resulting in ulcerations. Micro-tears on the feet of diabetics create minuscule portals of entry for various pathogens. Some of the bacterial organisms that enter these tears may originate from fecal material or are located in community showering/bathing facilities and then infect the feet of diabetics. Cross contamination between healthy family members and diabetics of opportunistic fungi may occur. These opportunists cause no problems in healthy individuals, but can start the infectious cascade in diabetic patients, eventually resulting in ulcerations and amputation. If diabetic patients are not careful to examine their feet daily, an infection can occur and become serious within a short period of time. The micro-tears might be caused by dermatophytes as well. Richard and Hare (1999) note that neglected tinea pedis, resulting in cracks and fissures, allows for secondary infection that can result in serious deep space infections in

diabetics[25]. They also found that high-risk diabetics with lower extremity neuropathy have a higher risk of complications from onychomycosis[25]. They suggest oral anti-fungal therapy and continued use of topical anti-fungal drugs be utilized for patients where this problem has been initially diagnosed[25].

Preliminary data from a study conducted at Weber State University on microbial succession that can result in interdigital bacterial infections of the diabetic=s foot indicates a role for dermatophytes (opportunistic/pathogenic fungi). LOPROX treatment produced a 58% reduction in patients with confirmed opportunistic fungi in the interdigital spaces. Patients who had opportunistic fungi in/on toenails showed an 87% decrease following treatment with LOPROX.

Observations in the Weber State University study also showed an association between opportunistic fungi and certain species of bacteria including *Staphylococcus aureus, Pseudomonas* species, and *Micrococcus sedentarius* among others. These bacteria, routinely tested for in clinical laboratories, can serve as sentinel organisms indicating possible dermatophytic infections that could eventually lead to ulcerations with the accompanying complications. Although most podiatrists do not test for these underlying dermatophytes, routine bacterial screening can reveal the presence of these sentinel bacteria so that appropriate treatment

can be administered. Kates et al. (1990) also observed this association between the prevalence of dermatophytes and these bacteria, along with *Brevibacterium epidermidis* and *Cornyebacterium minutissimum*[26]. Unfortunately, screening for these two organisms is not routine in some clinical laboratories. In addition, they also found an increase in *Candida* isolates correlated with isolation of other dermatophytes[26]. Anti-fungal prophylaxis would probably be warranted if these bacteria, or opportunistic dermatophytes, were found, decreasing the

synergistic effect of these organisms in ulceration development.

Screening for these sentinel bacteria may provide a diagnostic advantage for the podiatrist since isolation and cultivation of dermatophytes alone is difficult and expensive. Detection of sentinel bacteria also allows for continued monitoring to determine effectiveness of prophylactic anti-fungal treatments. Since many dermatophytes produce antibiotics, these can select for resistant strains of bacterial pathogens, along with promoting the emergence of newly resistant strains[26]. Control of opportunistic fungi decreases the opportunity for development and sustained selection of resistant bacteria[26].

Mechanism of Action of LOPROX

Ciclopirox is a synthetic, broad-spectrum hydroxypyridone anti-fungal, anti-bacterial and anti-inflammatory agent that differs chemically and mechanistically from other anti-fungal drugs in the azoles and allylamine classes[21-24]. Ciclopirox kills fungi by chelation of polyvalent cations and inhibitions of metal dependent enzymes including those responsible for degradation of peroxides[21,23,24]. Other anti-mycotics only alter steps in the sterol biosynthesis of fungal membrane. Ciclopirox primarily affects iron-dependent enzyme systems, such as cytochromes, catalase, and peroxidase. It also impairs the activity on mitochondrial hemoproteins by binding with iron, thus killing the cell organism[21-24]. Ciclopirox affects the cytoplasmic membrane as well, where it appears to impair active transport mechanisms, cell respiratory processes, and membrane integrity, and also negatively influences the macromolecular synthesis of nucleic acids and proteins[21,22,24].

Clinically, LOPROX (ciclopirox 0.77%) demonstrates powerful anti-fungal activity[22,24]. A 1% preparation of ciclopirox was shown to penetrate all layers of the stratum corneum of

human skin and inhibit the growth of *Trichophyton mentagrophytes*. It also has proven *in vitro* fungicidal activity against *Trichophyton rubrum, Epidermophyton floccosum, Candida albicans,* and *Microsporum canis*[27]. Thus, it is reasonable to propose that ciclopirox=s anti-fungal, anti-inflammatory, and anti-bacterial properties can reduce the number of foot infections by inhibiting potential pathogen colonization and reduce the likelihood of their recurrence in diabetic patients.

Conclusion

Emerging research supports the observation that aggressive prophylactic care including, the use of LOPROX, could result in fewer lower extremity amputations and a higher quality of life for patients with diabetes. LOPROX=s anti-fungal, anti-inflammatory, and anti-bacterial properties can provide effective treatment for foot ulcers thus reducing amputations in diabetic patients.

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