

Treatment of onychomycosis with dilute topical povidone-iodine in a dimethylsulfoxide solvent system

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Abstract

Introduction: Novel solutions of dilute povidone-iodine and dimethylsulfoxide have been employed in our practice for the treatment of onychomycosis. A retrospective review of our clinical experience with this regimen was undertaken to evaluate the tolerability and efficacy of this therapy and to determine if further prospective study may be beneficial.

Methods: An IRB-approved retrospective chart review of all patients employing this therapy in our practice for at least 24 weeks was completed. Clinical examination findings and microbiological culture results were analyzed for all patients before and after completion of 24 weeks of therapy.

Results: A total of thirteen patients were identified and all thirteen were included in this report. None discontinued use due to intolerance. There were no reported adverse events. The Onychomycosis Severity Index was used to assess both initial involvement and improvement at the 24-week time point. Pre-treatment fungal cultures were positive in all thirteen patients. Post-treatment fungal cultures were positive in five patients.

Conclusion: In this retrospective review, onychomycosis patients topically treated with dilute povidone-iodine solutions have experienced both subjective and objective improvement. Toxicity of the dilute topical povidone-iodine regimen was not observed or reported. Further prospective, controlled studies of aqueous topical povidone-iodine solutions for onychomycosis and paronychia are warranted.

Introduction

Onychomycosis is one of the most common nail disorders observed by dermatologists, primary care providers and podiatrists. It is a condition in which a fungal infection involving the nail plate and nailbed causes disfigured and discolored nails with frequent disruption of the normal nail bed/nail plate architecture. Both incidence and prevalence are on the rise, with an estimated 35 million Americans affected [1-3]. All infections are initiated with some sort of trauma to the nail plate, nail bed, proximal/lateral nail folds or hyponychium. This trauma allows the fungi to access the nail bed, where it slowly proliferates causing the stratum corneum of the nail bed to slowly become hyperkeratotic, often resulting in onycholysis. The infection also involves the nail folds and nail plate. The nail may become thickened, dystrophic, cracked, discolored and painful.

Certain conditions may predispose individuals to onychomycosis. Immunodeficiency, poor peripheral circulation and diabetes are frequent co-morbidities [4]. Likelihood of infection also increases with age as the rate of nail growth declines in older populations. Frequent trauma from athletics or grooming practices has also been associated with higher rates of persistent fungal infection of the feet and toe nails [5]. Males used to be more frequently affected than females, but with the increase in popularity of pedicures the incidence in females has risen to nearly equal levels.

Onychomycosis is most frequently caused by fungi of the dermatophyte family. Dermatophytes thrive in dark, moist, warm environments which explains why infection is seen more commonly

in toenails than in fingernails, as feet are often occluded in shoes for lengthy periods of time. Definitive diagnosis is typically obtained via fungal culture of the nails performed in the office setting, which allows for speciation as well.

Current treatment options for onychomycosis are marginally successful at best. There are oral and topical prescription and topical non-prescription treatment options available, but none have proven to be consistently effective. The FDA has approved one prescription nail lacquer (ciclopirox; Penlac[®], Sanofi Aventis), which has a cure rate of less than 10% [6]. The FDA-approved oral treatments terbinafine (Novartis, Lamisil[®], Basel, Switzerland) and itraconazole (Janssen, Sporonox[®], Titusville, NJ) have cure rates ranging from 30-40%, though definition of "cure" is inconsistent among published studies [7,8]. Systemic therapies also have inherent risk of hepatotoxicity and hematologic toxicity [9]. Over the counter options have not demonstrated any higher success rates than prescription drugs. All therapeutic approaches require lengthy treatment periods (often greater than one year), high patient compliance and high cost. The largest barrier in effective treatment of onychomycosis is the inability of the anti-fungal agent to reach the true nidus of infection, the subungual space and nail

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plate, due to difficulty of penetration. To date no systemic or topical therapy has emerged as a clearly superior choice for first-line therapy is these common, intractable infections. We have employed aqueous dilute povidone-iodine solutions in dimethylsulfoxide (DMSO) in an effort to eradicate the nidus of fungal infection with a novel therapeutic approach.

Patients and methods

IRB approval was obtained to perform a retrospective chart review of patients treated at the Bryn Mawr Skin and Cancer Institute with dilute solutions of 1% povidone-iodine (w/w) in aqueous dimethyl sulfoxide (DMSO) twice daily for at least 24 weeks. All patients were known to our practice and had been previously diagnosed with onychomycosis according to published practice guidelines [10]. All identified cases had positive pre-treatment fungal cultures (Table 1). Pre-treatment degree of severity was determined using the Onychomycosis Severity Index (OSI) [11]. The OSI score is obtained by multiplying the score for the area of involvement (range, 0-5) by the score for the proximity of disease to the matrix (range, 1-5). Ten points are added for the presence of a longitudinal streak or a patch (dermatophytoma) or for greater than 2 mm of subungual hyperkeratosis. Mild onychomycosis corresponds to a score of 1 through 5; moderate, 6 through 15; and severe, 16 through 35.

The treatment consisted of applying the 1% PVP-I/DMSO solution twice daily to the nail folds, subungual space and nail plate itself. Patients were instructed to allow the solution to absorb and dry for one minute before dressing with socks and shoes.

The aqueous DMSO solvent was chosen due to its penetration enhancing ability and its well-described non-toxicity [12-14]. The PVP-I concentration was chosen based on reported antimicrobial efficacy along with the known pharmaceutical chemistry of povidone-iodine topical solutions [15,16]. Patients were typically evaluated at 24-week intervals as per office routine. Fungal cultures were again obtained at the follow-up visit and the OSI was re-evaluated.

Results

A total of thirteen patients were identified and included in this retrospective study. Patient demographic, clinical and mycological data are detailed below (Table 1). None of the patients discontinued use due to intolerance. There were no reported adverse reactions to topical application of PVP-I/DMSO solution. The severity of Onychomycosis

was graded both pre-treatment and after 24 weeks of BID use using the OSI as being mild, moderate or severe with the corresponding numerical score. Pre-treatment and post-treatment culture results were determined by using Mycosel® culture medium.

Discussion

Topical onychomycosis treatment strategies require lengthy courses of therapy (i.e. >12 months) in order to allow the infected tissues to grow out and be replaced by newly deposited healthy nails. Anti-fungal resistance to the treating agent frequently develops during these extended treatment periods required by the inherently slow growth rate of the infected nails. Anti-fungal resistance and poor topical response rates are further complicated by the inability of most topical agents to effectively penetrate the subungual and periungual infectious tissues. This leads to chronic re-infection, even during treatment, and contributes the extremely low success rates of most onychomycosis therapies [17]. In addition to the commonly seen onychomycosis, the more infrequent but related problem of paronychia may also benefit treatment with an aqueous, non-toxic, antiseptic topical agent that can penetrate the periungual space [18].

Povidone-iodine (PVP-I) is a well-known, non-toxic, commonly used topical antiseptic with no reported incidence of fungal resistance. The efficacy of low-concentration iodophor systems has been well described both *in vitro* and *in vivo* including both planktonic and biofilm-related infections [19]. This is the first known series combining low dose iodophors, in this case povidone-iodine, with an aqueous DMSO delivery system capable of penetrating the superficial skin structures. This enables efficient delivery of the active agent to the subungual and periungual spaces. It is observed that by treating these subungual and periungual infectious foci, the re-infection of the nail plate during the long therapeutic course is prevented allowing the newly deposited nail to grow out in a fungus-free environment. Our results in this case series address this point. All 13 patients demonstrated positive cultures prior to initiation of treatment. At the 24-week point of treatment, 8/13 patients (62%) had negative culture results. The 5 patients that had positive culture results had baseline severe or moderate infections according to the OSI scale, with 2 patients having dermatophytomas present. Current therapies have been unable to access the masses of fungal hyphae that comprise the dermatophytoma, rendering this subset of infection the most difficult to treat. Of note, one of the patients with negative fungal culture at the 24-week time point also had a dermatophytoma present at the initiation of treatment. This

Table 1. Patient Demographic, Clinical and Mycological Data.

Patient	Age	Gender	OSI category/score		Culture- Week 0	Culture- Week 12
			Week 0	Week 24		
01	53	F	Severe/30*	Severe/26	Positive**	Positive**
02	49	F	Moderate/6	Mild/3	Positive**	Negative
03	47	F	Moderate/15	Moderate/13	Positive**	Positive**
04	71	F	Severe/17	Moderate/14	Positive**	Positive**
05	62	F	Severe/17	Severe/16	Positive**	Negative
06	36	F	Moderate/7	Moderate/6	Positive***	Negative
07	67	F	Severe/20*	Severe/18	Positive**	Positive**
08	57	M	Moderate/15	Moderate/10	Positive**	Negative
09	60	F	Mild/5	Mild/3	Positive**	Negative
10	65	M	Severe/20*	Severe/10	Positive**	Positive**
11	67	M	Severe/18*	Severe/16	Positive**	Negative
12	33	M	Mild/3	Mild/2	Positive***	Negative
13	31	M	Moderate/6	Mild/5	Positive**	Negative

*Indicates the presence of dermatophytoma (mass of fungal hyphae present within the nail represented by a thick yellow streak in the nail). **Culture positive for Trichophyton mentagrophytes. ***Culture positive for Trichophyton rubrum.

nail sign has been major impedance to effective treatment in the past and suggests this novel combination has the potential ability to access the nidus of infection that any other therapy has failed to do. None of the patients demonstrated complete eradication of the infection according to the OSI scale, but this is not unexpected as onychomycosis infections often take 48 weeks or longer to demonstrate cure in both the clinical and mycologic setting.

Another surprising result is the speed in which patients noted improvement of their infected toenails. Numerous patients claimed embarrassment at the sight of their toes and refused to wear open toed shoes in seasonal climates. After 24 weeks of therapy many patients noted an improvement in color of the nail itself and all of the patients wished to continue treatment past the 24 weeks point, as they were pleased with the improvement noted. Though we did not design the current study to assess the treatment effect on *Pseudomonas*, we suspect efficacy in this common co-morbid infection as well. It is important to keep in mind that these subjective results may be biased, as only patients that feel socially stigmatized or uncomfortable by the condition seek medical treatment.

Observation in our single center of 1% PVPI solutions in DMSO has been encouraging when used to treat onychomycosis. Further prospective studies of this topical system are being pursued for onychomycosis and paronychia.

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