Using Olivamine Containing Products to Reduce Pruritic Symptoms Associated With Localized Lymphedema

Darlene McCord, Ph.D., FAPWCA, Jane Fore, MD, FAPWCA

Abstract

Localized lymphedema in obese patients results in numerous symptoms associated with skin breakdown. One of the symptoms that most affects the patient being treated is pruritus, or itch. The pruritic response in skin can be extremely intense, causing severe pain and discomfort for long periods of time. The prominent biochemical trigger responsible for pruritus is the degranulation of DMCs and the subsequent release of HA. In addition, secondary biochemical factors present in infected and inflamed skin lower the threshold for DMC degranulation and potentiate the itch provoked by HA. Nine morbidly obese patients with mild to severe pruritus associated with localized lymphedema were evaluated over a six month period. All patients followed a treatment regimen that utilized several advanced skin care products. At the end of the study, 95% of the patients' pruritic symptoms were completely resolved. In fact, 7 out of 9 patients reported that their pruritic symptoms had disappeared in a matter of days. The treatment regimen provided numerous beneficial nutrients that reduced overall HA activity and inhibited the secondary biochemical mediators associated with pruritus. Additional research should be completed in order to further improve patient quality of life by diminishing the agony and discomfort that accompanies lymphedema-induced pruritus.

Introduction

Lymphedema is a chronic condition characterized by edema, which is usually localized in the limbs, trunk and genitalia[1]. The World Health Organization estimates that 45 million people have symptoms associated with lymphedema[2]. Recent literature has focused on the treatment of massive localized lymphedema in morbidly obese patients[3,4]. Lymphedema associated with obesity is most commonly localized in the lower limbs and the abdominal pannus[5]. Swelling induces chronic venous insufficiency. Venous return is initially compensated for by the lymphatic system but continual overload results in lymphatic failure and gives rise to venous and lymphatic edema.

Localized lymphedema in obese patients results in numerous symptoms associated with skin breakdown. One of the symptoms that most affects the patient being treated is pruritus, or itch. Managing and understanding the pathology of lymphedema has become increasingly relevant to symptoms associated with lymphedema in the extended care setting[6,7]. The reduction of lymphatic drainage induces a build up of inflammatory mediators in the skin. The accumulation of immune proteins and cytokines, in addition to venous and lymphatic edema, results in barrier dysfunction[8]. Improper barrier function eventually leads to infection and dermatitis, which may induce an intense pruritic response[9,10]. The reaction involves several communication cascades between numerous biochemical mediators and the peripheral nervous system.

Accepted for publication in Advances in Skin & Wound Care

Background

The pruritic response in skin can be extremely intense, causing severe pain and discomfort for long periods of time[11]. The prominent biochemical trigger responsible for pruritus is the degranulation of dermal mast cells (DMCs) and the subsequent release of histamine (HA)[12,13]. HA, or imidazolethylamine, is a biogenic amine present in numerous metachromatic granules in DMCs. When released, HA acts on endothelial H1 nerve receptors and elevates the concentration of cyclic adenosine monophosphate (cAMP) in the primary neurons. An expansion of the capillaries occurs, along with local edema and an increase in the volume of the vascular bed. The cAMP signaling pathway excites pruritic C-nerve fibers near the dermal-epidermal junction, thus inducing pruritus[14,15]. Circulating HA is eventually inactivated by the liver via several methylation and oxidation reactions.

In addition, secondary biochemical factors present in infected and inflamed skin lower the threshold for DMC degranulation and potentiate the itch provoked by HA. Prostaglandin E_2 (PGE2) is a biologically active carbon-20 unsaturated fatty acid and short range autocoid. PGE2 is a metabolite of arachidonic acid (AA) produced via the prostaglandin (PG) pathway[14,16]. AA is a polyunsaturated fatty acid derived from dietary sources and stored in the cell membrane fraction. The acid is primarily esterified to the phospholipids at the sn-2 position until phospholipase catalyzes its release[17,18]. Cyclooxygenase enzymes oxidize AA along the PG pathway to form prostaglandin D_2 (PGD2), PGE2, and prostaglandin F_2 (PGF2). Once released, PGE2 dilates the local capillary system and lowers the threshold for HA release[19].

Similarly, leukotriene B_4 (LKB4), leukotriene C_4 (LKC4), leukotriene D_4 (LKD4), and leukotriene E_4 (LKE4) are all AA metabolites and chemical mediators for inflammation and pruritus. However, unlike PGs, which can play important roles as biological regulators, the actions of leukotrienes (LKs) appear to be exclusively of a pathological nature. LKs are synthesized by the enzymatic oxidation of AA through the 5-lipoxygenase pathway[17,18]. LKs constitute a slow releasing substance discharged by DMCs after an IgE-antigen reaction[20]. LKB4, LKC4, LKD4, and LKE4 bind to cysteinyl-LK receptor-1 and cysteinyl-LK receptor-2, thus invoking inflammation and pruritus. In particular, LKB4 agitates pruritic C-nerve fibers and lowers the threshold for DMC degranulation[14,21].

Methodology

Treatment Group

Nine morbidly obese patients with mild to severe pruritus associated with localized lymphedema were evaluated over a six month period. The localized lymphedema presented either on the lower extremities or on the abdominal pannus. Pruritic symptoms were evaluated on an initial physician visit and followed carefully throughout the entirety of the study period. A final evaluation was give by the physician at the end of the six

month period. All patients were treated in the office and additionally given products that were part of the treatment regimen to take home for self-care. Physician and patient followed a regimen based upon location and severity of lymphedema, as well as the intensity of the patient's skin breakdown and associated pruritus.

Treatment Regimen

- Cleanse with Olivamine-based Cleansing Lotion and then pat dry.
- Spray area with Olivamine-based Antimicrobial Spray.
- If skin is macerated and infected, apply Olivamine-based Calazime Protectant Paste.
  OR
  If skin is dry and flaky, use gentle strokes to apply a small amount of Olivamine-based Skin Repair Cream followed by Olivamine-based Nutrashield Cream.
- Lightly dust area with Antifungal Powder, as indicated.

Treatment Evaluation

Pruritus Intensity	**Lymphedema Severity[2,7]**
0-Absent	1-Mild (< 20% increase)
1-Mild	2-Moderate (20-30% increase)
2-Mild-Moderate	3-Severe (>30% increase)
3-Moderate	
4-Moderate-Severe	
5-Severe	

Table I. Pruritic intensity was evaluated subjectively based on patient description and attending physician's notes. Lymphedema severity was determined by the percent increase of edema in the specified location[2,7].

Results

Approximately 95% of the patients' pruritic symptoms were completely resolved in 6 months. In fact, 7 out of 9 patients reported that their pruritic symptoms had disappeared in a matter of days. The average evaluation score for pruritus intensity before treatment was 2.22, which corresponds to a discomfort level in between mild-moderate and moderate. After treatment with Olivamine-based advanced skin care products, the average evaluation score was 0.11, which corresponds to a discomfort level scarcely above absent.

Patient	Lymphedema Location	Lymphedema Severity	Pruritus Intensity (Before Treatment)	Pruritus Intensity (After Treatment)
B.B.	Legs	2	3	0
R.F.	Pannus	3	3	0
L.K.	Legs	2	5	0
H.M.	Pannus	3	1	0
E.M.	Pannus	1	1	0
D.M.	Pannus	3	2	0
D.V.	Pannus	3	1	0
E.R.W.	Legs	3	1	0
E.W.	Legs	3	3	1

Table II. The pruritic symptoms of nine obese patients suffering from localized lymphedema were evaluated over a six month period. The lymphedema presented on the lower legs or on the abdominal pannus. Pruritic symptoms were evaluated on an initial and final physician visit, as well as throughout the entirety of the study period.

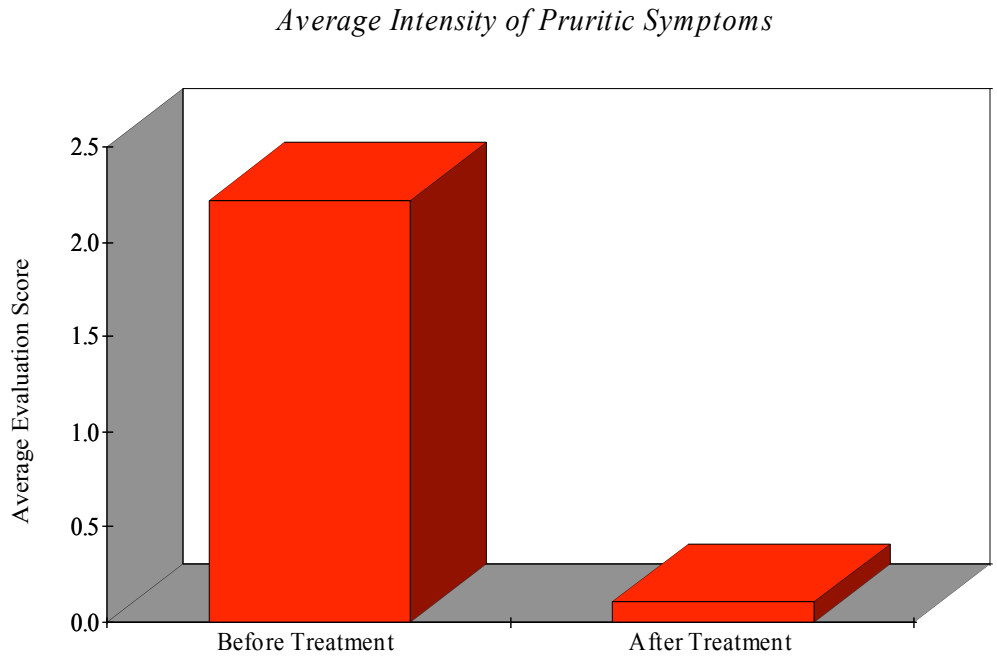

Figure I. Approximately 95% of all patients' pruritic symptoms were completely resolved in 6 months. The average evaluation score for pruritus intensity before treatment was 2.22, which corresponds to a discomfort level in between mild-moderate and moderate. After treatment, the average evaluation score was 0.11, which corresponds to a discomfort level just above absent.

Discussion

Olivamine-based skin care products contain several specialized nutrients that effectively modulate the biochemical abnormalities associated with pruritus. The anti-pruritic nutrients include hydroxytyrosol (HT), or 3,4-dihydroxyphenyl ethanol, which is a simple phenol found predominantly in Olea europea, or the olive plant. HT is an extremely potent free radical scavenger that stimulates significant anti-inflammatory activity in skin[22]. Numerous studies have established that topically applied antioxidants substantially reduce pruritus by inhibiting the secondary biochemical factors present in infected and inflamed skin[23]. In particular, HT inhibits LKB4 generation by modulating the enzymatic oxidation of AA through the 5-lipoxygenase pathway[24,25]. Altogether, the phenolics found in HT possess an array of beneficial LK-inhibitory, PG-sparing, and antioxidant properties[26].

In addition, Olivamine containing products provide aloe barbadensis leaf juice, niacinamide (NA), pyridoxine (PO) and retinyl palmitate (RP). Aloe barbadensis leaf juice contains the glycoprotein alprogen, which has been found to inhibit multiple signals throughout the biochemical cascade responsible for DMC degranulation. Most notably, alprogen inhibits HA activity and prevents the release of LKB4[27,28]. NA and PO induce a similar inhibitory activity of DMC degranulation and HA release[29,30]. Furthermore, NA has been shown to significantly inhibit cAMP at the dermal-epidermal junction, thus reducing the excitation of pruritic C-nerve fibers[31,32]. RP reduces pruritic symptoms associated with vitamin A deficient inflammation. Numerous studies show that vitamin A deficiency aggravates the clinical manifestations of inflammatory reactions, thereby increasing the release of pruritic inducing PGs and LKs[33,34]. The topical application of RP prevents vitamin A deficiency and subsequently reduces inflammation and pruritus.

Nutrashield Cream and Skin Repair Cream are composed of advanced silicones that prevent the excessive transepidermal water loss (e-TEWL) responsible for dry, irritated skin. Transepidermal water loss (TEWL) is a measure of cutaneous barrier function reflecting skin water content and is defined as grams of water lost per square meter of skin per hour[35]. TEWL decreases stratum corneum hydration and activates a pruritic inflammatory response in the epidermis and dermis[36]. In addition, scratching dry, irritated skin further increases TEWL and intensifies the associated pruritus[37]. An independent *in vitro* study found that silicone-based Nutrashield Cream and Skin Repair Cream significantly reduced e-TEWL, conserving nearly four times the quantity of water as the control[38]. Reducing TEWL and conserving stratum corneum hydration is the key to reducing the dry, irritated skin responsible for inflammation and pruritus[39].

Conclusion

Olivamine containing skin care products effectively treat the pruritic symptoms associated with localized lymphedema. In fact, 95% of the pruritic symptoms reported by the patients were completely dissolved at the end of six months. The majority of patients, who had experienced chronic lymphedema-induced pruritic symptoms for

several years, drastically improved in a matter of days. Olivamine-based products provide numerous beneficial nutrients that reduce overall HA activity, while inhibiting the secondary biochemical mediators associated with pruritus. Altogether, an Olivamine-based treatment regimen significantly improved patient quality of life by diminishing the agony and discomfort that accompanies lymphedema-induced pruritus. Further research is suggested in order to determine the most effective regimen for treating pruritic symptoms associated with localized lymphedema.

References

[1] Moffatt, C., P. Franks, D. Doherty, A. Williams, C. Badger, E. Jeffs, N. Bosanquet, and P. Mortimer. 2003. Lymphedema: an underestimated health problem. *Q. J. Med.* 96: 731-738.
[2] Bianchi, J., and M. Todd. 2000. The management of a patient with lymphedema of the legs. *Nursing Standard* 14(40): 51-56.
[3] Rockson, S. 2006. Lymphedema. *Curr. Treat. Options Cardiovasc. Med.* 8(2): 129-136.
[4] Ryan, T. 2003. On treatment of peripheral lymphedema. *Lymphology* 36(3): 110.
[5] Wu, D., J. Gibbs, D. Corral, M. Intengan, and J. Brooks. 2000. Massive localized lymphedema: additional locations and association with hypothyroidism. *Hum. Pathol.* 31(9): 1162-1168.
[6] Daroczy, J. 1995. Pathology of lymphedema. *Clin. Dermatol.* 13(5): 433-444.
[7] Becker, F. 2006. Lymphedema. *Rev. Med. Suisse.* 2(51): 323-324.
[8] Vaqas, B., and T. J. Ryan. 2003. Lymphedema: pathophysiology and management in resource-poor settings - relevance for lymphatic filariasis control programmes. *Filaria Journal* 2: 4-13.
[9] Elias, P. M., and K. R. Feingold. 2001. Does the tail wag the dog: role of the barrier in the pathogenesis of inflammatory dermatoses and therapeutic implications. *Arch. Dermatol.* 137: 1079-1081.
[10] Madison, K. C. 2003. Barrier function of the skin: "La Raison d'Etre" of the epidermis. *Journal of Investigative Dermatology* 121: 231-241.
[11] Stander, S., and M. Steinhoff. 2002. Pathophysiology of pruritus in atopic dermatitis: an overview. *Experimental Dermatology*. 11:12-24
[12] Darsow, U., J. Ring, E. Scharein, and B. Bromm. 1996. Correlations between histamine-induced wheal, flare and itch. *Arch. Dermatol. Res.* 288(8): 436-441.
[13] Lugon, J. 2005. Uremic pruritus: a review. *Hemodial. Int.* 9(2): 180-188.
[14] Hart, P., S. Townley, M. Grimbaldeston, Z. Khalil, and J. Finlay-Jones. 2002. Mast cells, neuropeptides, histamine, and prostaglandins in UV-induced systemic immunosuppression. *Methods.* 28(1): 79-89.
[15] Reinisch, C., and E. Tschachler. 2005. The touch dome in human skin is supplied by different types of nerve fibers. *Ann. Neurol.* 58(1): 88-95.
[16] Hagermark, O., and K. Strandberg. 1977. Pruritogenic activity of prostaglandin E2. *Acta. Derm. Venereol.* 57(1): 37-43.
[17] Martin-Venegas, R., S. Roig-Perez, and J.J. Monero. 2006. Arachidonic acid cascade and epithelial barrier function during Caco-2 cell differentiation. *J. Lipid Res.*
[18] Needleman, P., J. Truk, B.A. Jakschik, A.R. Morrison, and J.B. Lefkowith. 1986. Arachidonic Acid Metabolism. *Annual Review of Biochemistry*. 55: 69-102.

[19] Peharda, V. F. Gruber, M. Kastelan, I. Brajac, and L. Cabrijan. 2000. Pruritus an important symptom of internal diseases. *Dermatovenerologica.* 9(3): 1-12
[20] Andoh, T., and Y. Kuraishi. 2000. Involvement of blockade of leukotriene B(4) action in anti-pruritic effects of emedastine in mice. *Eur. J. Pharmacol*. 406(1): 149-152.
[21] Andoh, T., N. Katsube, M. Maruyama, and Y. Kuraishi. 2001. Involvement of leukotriene B_4 in substance P-induced itch associated response in mice. *Journal of Investigative Dermatology*. 117: 1621-1626.
[22] Bitler, C.M., T.M. Viale, B. Damaj, and R. Crea. 2005. Hydrolyzed olive vegetation water in mice has anti-inflammatory activity. *J. Nutr.* 135(6): 1475-1479.
[23] Hadshiew, I., F. Stab, S. Untiedt, K. Bohnsack, F. Rippke, and E. Holzle. 1997. Effects of topically applied antioxidants in experimentally provoked polymorphous light eruption. *Dermatology*. 195(4): 362-368.
[24] Petroni, A., M. Blasevich, N. Papini, M. Salami, A. Sala, and C. Galli. 1997. Inhibition of leukocyte leukotriene B4 production by an olive oil-derived phenol identified by mass-spectrometry. *Thromb. Res.* 87(3): 315-322.
[25] Kohyama, N., T. Nagata, S. Fujimoto, and K. Sekiva. 1997. Inhibition of arachidonate lipoxygenase activities by 2-(3,4-dihydroxyphenyl)ethanol, a phenolic compound from olives. *Biosci. Biotechnol. Biochem.* 61(2): 347-3350.
[26] de la Puerta, R., V. Ruiz Gutierrez, and J.R. Hoult. 1999. Inhibition of leukocyte 5-lipoxygenase by phenolics from virgin olive oil. *Biochem. Pharmacol.* 57(4): 445-449.
[27] Ro, J.Y., B.C. Lee, J.Y. Kim, Y.J. Chung, M.H. Chung, S.K. Lee, T.H. Jo, K.H. Kim, and Y.I. Park. 2000. Inhibitory mechanism of aloe single component (alprogen) on mediator release in guinea pig lung mast cells activated with specific antigen-antibody reactions. *J. Pharmacol. Exp. Ther.* 292(1): 114-121.
[28] Graf, J. 2000. Herbal anti-inflammatory agents for skin disease. *Skin Therapy Lett.* 5(4): 3-5.
[29] Garcia, M., and R. Gonzalez. 1979. Effect of pyridoxine on histamine liberation and degranulation of rat mast cells. *Allergol. Immunopathol. (Madr.)*. 7(6): 427-432.
[30] Alvarez, Ricardo Gonzalez, and Milagros Garcia Mesa. Asorbic acid and pyridoxine in experimental anaphylaxis.
[31] Cosmetic Ingredient Review Expert Panel. Final report of the safety assessment of niacinamide and niacin. Int. J. Toxicol. 2005;5:1-31.
[32] Bissett D, Miyamoto K, Sun P, Li J, Berge C. Topical niacinamide reduces yellowing, wrinkling, red blotchiness, and hyperpigmented spots in aging facial skin. International Journal of Cosmetic Science 2004;26(5):231-8.
[33] Wiedermann, U., X.J. Chen, L. Enerback, L.A. Hanson, H. Kahu, and U.I. Dahlgren. 1996. Vitamin A deficiency increases inflammatory responses. *Scandinavian Journal of Immunology*. 44: 578.
[34] Gatica, L., S. Alvarez, N. Gomez, M.P. Zago, P. Oteiza, L. Oliveros, and M.S. Gimenez. 2005. Vitamin A deficiency induces prooxidant environment and inflammation in rat aorta. *Free Radic. Res.* 39(6): 621-628.
[35] Ostlere, L.S., C. Taylor, R. Baillod, and S. Wright. 1994. Relationship between pruritus, transepidermal water loss, and biochemical markers of renal itch in haemodialysis patients. *Nephrol. Dial. Transplant.* 9(9): 1302-1304.

[36] Fujii, M., T. Nabe, J. Tomozawa, and S. Kohno. 2006. Involvement of skin barrier dysfunction in itch-related scratching in special diet-fed hairless mice. *Eur. J. Pharmacol*. 530(1-2): 152-156.
[37] Miyamoto, T., H. Nojima, T. Shinkado, T. Nakahashi, and Y. Kuraishi. 2002. Itch-associated response induced by experimental dry skin in mice. *Jpn. J. Pharmacol*. 88(3): 285-292.
[38] McCord, D. 2004. *Using Remedy Nutrashield to Prevent Transepidermal Water Loss.*
[39] Grubauer, G., P. M. Elias, and R. Feingold. 1989. Transepidermal water loss: the signal for recovery of barrier structure and function. *Journal of Lipid Research.* 30: 323-333.