

Molecular Medicine Letters

Could Low-Dose Naltrexone be an Effective Treatment for Hailey-Hailey Disease?

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Rec date: June 30, 2016; Acc date: July 15, 2016; Pub date: July 19, 2016

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Although originally described by the Hailey brothers in 1939, Hailey-Hailey disease (HHD), or familial benign chronic pemphigus, still does not have an established treatment method. Recent testimonial and anecdotal evidence suggest low-dose naltrexone (LDN) as an effective treatment for HHD. Naltrexone was originally approved by the US Food and Drug Administration in 1984 for the treatment of alcohol and opiate addiction. In lower doses (4.5 mg or less rather than 50 mg), naltrexone is being used to treat many diseases; however, there are no published studies on its long-term efficacy or for the treatment of HHD.

HHD is a rare genetic dermatosis, characterized by pruritic (itchy) vesicles, erosions, weeping plaques, fissures and scale crust. The most common affected areas include the axillae, perineum, groin, neck, and inframammary folds [1,2]. These symptoms interfere with physical activity and dramatically affect quality of life [2,3]. The prevalent mechanism of inheritance for HHD is known to be through haploinsufficiency of *ATP2C1*. Despite the studies on *ATP2C1* and its relation to HHD, few treatment options currently exist for HHD. Physicians rotate through numerous treatment options including corticosteroids, retinoids, cyclosporin, vitamin D3, and tacrolimus in the hopes of finding a treatment that improves a patient's condition. In intractable cases, physicians struggle due to the limited effective treatment options, while the patient continues to struggle with the debilitating symptoms and deteriorating quality of life.

A potential effective and inexpensive treatment method may be LDN. Naltrexone acts as a non-selective antagonist of opioid receptors blocking them temporarily. This blockade appears to lead to the up regulation of mood-enhancing endogenous opioids and dopamine activity, which favors more methionine enkephalin binding and results in increased immune function [4,5].

LDN has been shown to be beneficial in a large number of diseases including fibromyalgia [6-8], multiple sclerosis [9-11], HIV [12,13], Crohn's disease [14], and adenoid cystic tongue carcinoma [15] (Table 1). Clinical trials for the use of LDN to treat fibromyalgia report that it is well tolerated and leads to a reduction in pain, improved mood, and increased satisfaction with life [6]. In fibromyalgia, LDN reduces the level of pro-inflammatory cytokines and neurotoxic superoxides produced by microglia cells in the central nervous system [7,8]. For multiple sclerosis patients, clinical trials show that LDN significantly improves pain, mental health and cognitive function [9]. A substantial improvement on spasticity was also observed in multiple sclerosis patients treated with LDN, seemingly as a result of increased beta endorphin levels [10]. In AIDS patients treated with LDN, an increase in beta endorphin levels is observed and levels of CD4 cells stabilized [13]. Additionally, LDN is beneficial for Crohn's disease patients, with 30% of LDN-treated patients and 18% of placebo-treated patients achieving a clinical remission in a randomized double-blind placebo-controlled trial in adults [14]. Similarly, 25% of pediatric patients treated with LDN achieved clinical remission

Condition	LDN Dosage	Length of study	Number of patients	Tolerability	Results	Publication
Atopic eczema	25 mg/day	Single treatment for 1 hour	11	Well tolerated. None of the subjects suffered from withdrawal symptoms.	Reduction in perifocal itch, reduction in itch duration, and intensity of itch diminished in naltrexone-treated patients.	Heyer et al., 2002
Cholestatic pruritus	50 mg/day	4 weeks	16	Well tolerated with no serious adverse events. Side effects included general malaise associated with nausea, dizziness, flushing, drowsiness, headache, nightmares, tremor, and mild abdominal cramps. Most side effects subsided after the first 3 days.	Reduction in daytime and nighttime itching, disturbed sleep, and fatigue in patients receiving naltrexone treatment.	Wolfhagen et al., 1997
Cholestatic pruritus	50 mg/day	6–8 weeks	20	Well tolerated. Most side effects were consistent with opioid withdrawal-like phenomena and disappeared after 2 days of treatment.	Decrease in pruritus in naltrexone-treated group, with some patients achieving complete disappearance of pruritus.	Terg et al., 2002
Cholestatic pruritus	50 mg/day	2 weeks	34	Well tolerated. Most complications were mild and were related to withdrawal.	Decrease in pruritus in naltrexone-treated patients.	Man-sour-Ghanaei et al., 2006
Crohn's disease	4.5 mg/day	12 weeks	40	Well tolerated with no serious adverse events. Fatigue was the only side effect significantly more common in LDN-treated patients.	LDN-treated patients showed 70-point decline in CDAI scores (a measure of clinical disease activity): 88% of LDN-treated patients achieved this CDAI decline compared to 40% of placebo-treated patients. Clinical remission in 25% of LDN-treated patients and 0% of placebo-treated patients. 67% of LDN-treated patients had improvement with mild disease activity. Systemic symptoms and social quality of life improved in LDN-treated patients.	Smith et al., 2011
Crohn's disease	0.1 mg/kg/day (≤4.5 mg/day)	8–16 weeks	14 (pediatric patients)	Well tolerated with no serious adverse events.	LDN-treated patients and 0% of placebo-treated patients. 67% of LDN-treated patients had improvement with mild disease activity. Systemic symptoms and social quality of life improved in LDN-treated patients.	Smith et al., 2013
Adenoid cystic tongue carcinoma	3–4.5 mg/day	ongoing (nearly 4 years at time of study)	1	Well tolerated with no complications from LDN.	Marked regression of tumor with remission of nearly 4 years and no clinical evidence of cancer.	Khan, 2014
Fibromyalgia	4.5 mg/day	22 weeks	31	No significant difference in tolerability between active drug and placebo. Vivid dreams and headache were more frequent in LDN-treated patients. No reports on tolerability.	Pain reduction, increased general satisfaction with life, and improved mood.	Younger et al., 2013
HIV	3 mg/day	12 weeks	158*	No reports on tolerability.	Stabilization of CD4 levels, arrest of disease progression, and significant reduction in incidence of opportunistic infections, with an increased survival in LDN-treated patients.	Bihari, 1995
Multiple Sclerosis	4.5 mg/day	8 weeks	80	Well tolerated with no serious adverse events. Vivid dreams were reported for LDN-treated patients.	Improvement in mental health, pain, and cognitive function.	Cree and Kornyeveva, 2010
Multiple Sclerosis	2–4 mg/day	6 months	40	Well tolerated. Most adverse events were minor: urinary infection, hematological abnormalities, irritability, mood alteration, joint pain, and gastrointestinal infection	Beneficial effect on spasticity.	Gironi et al., 2008
Pruritus associated with chronic eczema	50 mg/day	2 weeks	38	Well tolerated with a significant difference between placebo and naltrexone treatment groups. Main side effects were dizziness, nausea, vomiting, headache, and cramps.	Reduction of pruritus using VAS score in naltrexone-treated patients. Six patients in the naltrexone group achieved total remission of pruritus, whereas no patient in the placebo group achieved remission.	Malekzad et al., 2009

*This number represents number patients treated in clinic [and described in a letter to the editor] after a placebo-controlled trial (n=38) was carried out 1985-1986.

whereas no placebo-treated patients achieved remission in a pilot study [14].

Naltrexone has also shown promising results in the treatment of intractable pruritus. Patients with treatment-refractory cholestatic pruritus reported significant improvement with a higher dose of naltrexone (50 mg/day), and some were completely free of itching [16-18]. Similarly, naltrexone (25 or 50 mg/day) was effective in reducing pruritus associated with atopic dermatitis, with some patients experiencing total remission of pruritus [19,20]. Taken together, these results suggest that naltrexone has strong antipruritic effects. Accordingly, the European Guideline on Chronic Pruritus recommended the use of naltrexone and other opioid receptor antagonists for pruritus associated with cholestatic pruritus and atopic dermatitis [21].

HHD patients treated with LDN report up to 90% healed skin and a reduction in body weight, depression, and suicidal thoughts (if there is a secondary infection, patients report it is important to treat the infection in addition to LDN treatment for HHD) [22]. Despite these promising results, there are no published case studies or reports and no clinical studies are testing the use of LDN to treat HHD. These studies are necessary to better understand the mechanism of action and effects of LDN in HHD. LDN may be useful in the treatment of HHD by modulating the immune system by inhibiting opioid receptors, thereby increasing endorphin and enkephalin levels. Increased endorphin production can help with pain, spasticity, fatigue, and relapse rate. Moreover, opioid receptors on keratinocytes have been shown to promote wound healing by promoting the intercellular dissociation of keratinocytes and altering the migration pattern of these skin cells [23]. These data and patient testimonials suggest that LDN may be an effective treatment for HHD. However, many physicians hesitate to prescribe LDN because of the lack of published studies. The severity of complications from HHD is understated. Thus it is critical to conduct clinical studies to determine the efficacy of LDN in HHD with the goal of providing better treatment options for patients.

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