

## Low-Dose Naltrexone-Induced Remission in Hailey–Hailey Disease Maintained in Remission with Topical Combination of Ketamine and Diphenhydramine

### Abstract

Recent anecdotal evidence suggests that oral low-dose naltrexone (LDN) is effective for Hailey–Hailey disease (HHD) but suffers the limitation of immediate relapse following cessation of the medication. With lack of safety data on long-term administration of LDN, we explored the utility of a topical diphenhydramine/ketamine (DK) cream in maintaining the remission achieved with LDN. A 42-year-old male with treatment-refractory HHD remitted with 5 mg naltrexone/day but relapsed on stopping the drug. Symptoms abated after restarting LDN. The impact of regular twice-a-day application of a specially formulated DK cream containing diphenhydramine (2% w/w) and ketamine (1% w/w) over the affected areas on maintenance of remission was explored till the next relapse. Our approach enabled dose reduction of naltrexone to 3 mg/day without loss of treatment benefit. After 3-month overlap of naltrexone and DK cream, withdrawal of naltrexone maintained remission with only the topical regime with no adverse effects till 4 months of follow-up. The use of topical agents with anti-inflammatory, antipruritic, antinociceptive, and naltrexone-mimicking properties merits exploration as an option to provide short but significant period of naltrexone-free maintenance of remission to patients with HHD.

**Keywords:** Benign familial pemphigus, diphenhydramine, Hailey–Hailey disease, ketamine, low-dose opioid, naltrexone

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### Introduction

Hailey–Hailey disease (HHD) arises from a defect in keratinocyte adhesion possibly secondary to a primary defect in a calcium pump protein, ATP2C1.<sup>[1]</sup> The itchy, painful, and malodorous flexural lesions significantly impair patients' quality of life. Only temporary symptom alleviation has been reported with tried drugs.<sup>[1,2]</sup> Recent discovery of low-dose naltrexone (LDN) as a novel agent for HHD has sparked interest. The documented efficacy of LDN for HHD is offset by the immediate postcessation relapse,<sup>[2-5]</sup> prompting exploration of therapeutic options to maintain the remission achieved. We compounded a topical diphenhydramine/ketamine (DK) combination cream with anti-inflammatory, antipruritic, antinociceptive, and naltrexone-like effects. Our encouraging results merit exploration of this approach in properly designed studies to provide maintenance of remission to patients with HHD during naltrexone-free period(s).

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### Case Details

A 42-year-old male with biopsy-confirmed HHD of 8 years and a strong family history presented with erythematous, macerated, and eroded plaques over the groins [Figure 1a and b]. His medical history included topical and systemic steroids, antibiotics, dapsone, cyclosporine, and methotrexate; all had to be stopped owing to suboptimal response, relapse on cessation, and/or sustenance of drug-induced hepatic/renal dysfunction. The patient refused ablative therapies and botulinum toxin as treatment options. Oral naltrexone was initiated at 5 mg/day once at night after discontinuing other medications. One 50 mg naltrexone tablet was dissolved in 50 mL of distilled water in an amber-colored plastic container and left over for 2 h. The insoluble excipients that gave a cloudy appearance were filtered off to obtain a clear, relatively excipient-free solution containing 1 mg/mL of naltrexone.

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Confirmation of the expected drug concentration done by testing 1 mL solution with high-performance liquid chromatography-electrochemical detection revealed 0.99 mg/mL (almost 1 mg/mL). About 5 mL of the clear solution was administered to the patient after mixing with fruit juice to mask the bitter taste. The filtered stock solution was given to the patient to store in refrigerator at 4°C; stability was maintained for 60 days in contrast to less than 30 days at 25°C.<sup>[6]</sup>

Healing started within 2 weeks, with 90% improvement in lesions [Figure 1c and d], symptoms, and quality of life by 1 month. Hemogram and metabolic panel after 1 month of therapy revealed no abnormality over the baseline values. LDN (5 mg/day) was continued for 12 weeks, but new erosions developed within 2 weeks of cessation leading to recommencement of LDN (5 mg/day). We considered preparing a safe, corticosteroid-free topical formulation with potent anti-inflammatory, antipruritic, and naltrexone-mimicking properties. A nonirritant and stable DK cream containing diphenhydramine (2% w/w) and ketamine (1% w/w) specially compounded using pluronic lecithin organogel (PLO) as the vehicle base was given for regular twice-a-day application over the groins after a negative patch test. The application amount was around 2–2.5 mL on each side, with maximum 10 mL/day. The cream was started in the third week of having restarted the patient on 5 mg/day oral LDN. Three weeks later, LDN was tapered to 3 mg/day while DK cream was continued; this combination was continued for 3 months with sustained remission and no adverse effects (AEs).



**Figure 1:** (a and b) Clinical picture depicting the discolored macerated eroded plaques of Hailey–Hailey disease over the patient’s groins at baseline and (c and d) at third month after stopping of low-dose naltrexone (taken for 7 months) showing significant improvement in lesions maintained only on topical regime (c and d)

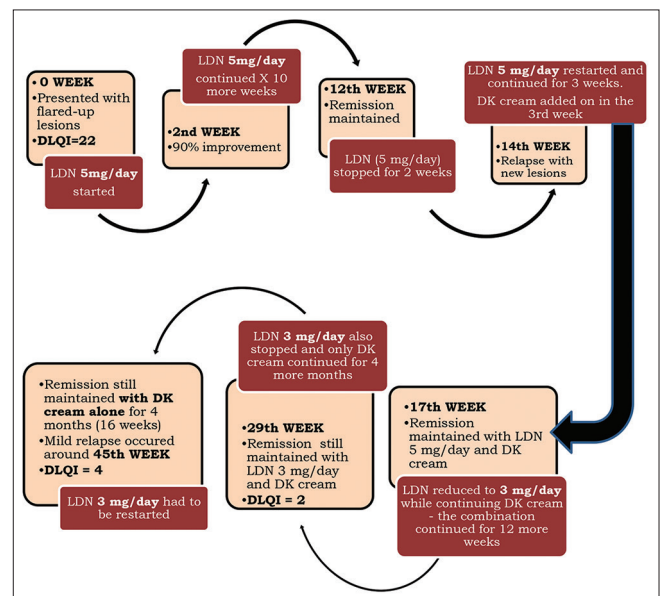
Thereafter, naltrexone was withdrawn while continuing DK cream. Surprisingly, the patient remained in remission for at least 4 more months requiring application of mometasone–mupirocin cream only on two occasions. On both occasions, swab from the mild discharge was negative for any bacterial growth on culture. However, after 4 months, LDN (3 mg/day) had to be restarted to control a gradually occurring mild but definite relapse. Patient’s Dermatology Quality of Life Index (DLQI) improved remarkably from 22 (before LDN) to 2 (after 7 months, till the continuation of LDN)) with mild increase to 4 during the 4-month naltrexone-free period. Figure 2 schematically summarizes the patient’s clinical course with details of changes made in the therapeutic protocol and response.

**Discussion**

Naltrexone, an inhibitor of  $\mu$ -opioid receptors, is approved by the United States Food and Drug Administration for opioid addiction management, typically given at a dose of 50–100 mg daily. In addition to its action on opioid receptors leading to wound healing, it is also a toll like receptor 4 (TLR4) antagonist which is responsible for correcting the calcium homeostasis.<sup>[7,8]</sup>

In the handful of studies conducted on use of LDN in HHD, relapse after cessation occurred in all.<sup>[2-5]</sup> Our current naiveté regarding long-term AEs of LDN prompted our quest for a maintenance agent. The topical DK regimen allowed naltrexone dose reduction and provided at least a 4-month LDN-free remission to the patient.

Topical diphenhydramine exerts potent antipruritic, anti-inflammatory, antibacterial and anesthetic effects and reinforces the epidermal barrier function.<sup>[9-11]</sup> Ketamine, a high-affinity antagonist of the glutamate



**Figure 2:** Schematic line diagram depicting the sequential changes made in the patient’s treatment protocol and corresponding effect on disease activity

N-methyl-D-aspartate receptor, exerts potent antinociceptive and anesthetic properties by various mechanisms especially stimulation of the  $\gamma$ -aminobutyric acid<sub>A</sub> receptors,<sup>[12,13]</sup> suppresses the release of proinflammatory cytokines through TLR4/2 inhibition, and mimics the biological effects of LDN.<sup>[13,14]</sup> Table 1 summarizes the biological effects of these agents.

Topical ketamine has been used with lidocaine and amitriptyline for various neuropathic pain-related and itchy disorders with well-established safety. Furthermore,

blood levels of ketamine in patients on topical ketamine have been reported as below detection level in multiple studies.<sup>[13]</sup> Currently, a safe amount of topical ketamine cannot be precisely specified owing to several factors determining systemic absorption such as concentration, vehicle (hydrogel > PLO > oil-in-water base), surface area covered, occlusion, and thinness of the skin. In a double-blind randomized controlled trial that compared the efficacy and safety of topical preparations of 2% amitriptyline, 1% ketamine, their combination, and

**Table 1: Putative mechanisms of action of diphenhydramine and ketamine contributing to their therapeutic benefit in Hailey–Hailey disease as a topical agent**

Site of action	Biological effect
<b>Diphenhydramine</b>	
H1/2r - (type 1 >> type 2)	Inhibition of H1r resulting in direct cutaneous antipruritic effect
Location - epidermal	
H1/2r	Improvement of epidermal barrier by opposing mast cell-derived histamine
Location - dermal mast cells	
Involucrin, loricrin, and filaggrin	Induction of expression of these <i>epidermal differentiation-related proteins</i> resulting in enhanced epidermal differentiation, leading to more robust corneocytes
	Overall impact - improved epidermal barrier repair
Epidermal HMG CoA reductase, serine palmitoyl transferase, FA2H, and the elongation enzyme (ELOVL4)	Increased synthesis of these enzymes leading to enhanced epidermal lipid synthesis
Epidermal-specific, transmembrane transporter, ABCA12 (that delivers glucosylceramides into nascent lamellar bodies)	Increased synthesis resulting in better lipid secretion by enhanced deposition of lamellar body contents at the stratum granulosum-corneum interface
Cell membranes of certain bacteria including <i>S. aureus</i> and <i>S. epidermidis</i>	Surfactant effect leading to altered permeability and function of bacterial membrane - bacteriostatic effect
<b>Ketamine</b>	
$\wedge$ NMDA receptor	Inhibition of the release of L-glutamate, which is present at a majority of excitatory synapses
GABA <sub>A</sub> receptor	Stimulation of the GABA <sub>A</sub> receptor
HCN1 pacemaker channels	*Induction of blockade of the channel
nNO synthase	**Activation of nNO synthase
$\mu$ and $\kappa$ opioid receptors - <i>simulation of naltrexone effect</i>	Delay in desensitization and improvement in resensitization of $\mu$ receptors
TLR4 - <i>simulation of naltrexone effect</i>	***Inhibition and reduction in the expression of TLR4 and 2
TLR2	
Cell adhesion molecules - CD11b, CD16, CD18, CD62L	Inhibition of the upregulation of CD18 and CD62L (in activated human neutrophils), and CD11b and CD16 (which bind to complement- or immunoglobulin-opsonized particles) resulting in reduction of leukocyte adherence and arrest of complement/immunoglobulin-mediated inflammatory cascade
NF-kB and AP-1	Suppression of activation of NF-kB and AP-1 resulting in inhibition of TNF- $\alpha$ gene expression

$\wedge$   
H1/2r=Histamine type 1/2 receptors; FA2H=Fatty acid 2-hydroxylase; ELOVL4=Elongation of very long-chain fatty acid-4; NMDA=Glutamate N-methyl-D-aspartate; GABA<sub>A</sub>= $\gamma$ -aminobutyric acid<sub>A</sub>; nNO=Neuronal nitric oxide; TLR=Toll-like Receptor; NF-kB=Nuclear factor-kappa B; AP-1=Activator protein,  $\wedge$ NMDA receptors are widely present in the peripheral nervous system; all sensorimotor axons bear them; cutaneous inflammation upregulates the NMDA receptors present over the peripheral neuronal axons, \*Blockade of HCN1 channels is probably the major mechanism that imparts ketamine its potent anesthetic property, \*\*Activation of nNO synthase also contributes to the anesthetic effect; activation of nNO synthase by ketamine stimulates the L-arginine/NO/cyclic GMP pathway to induce peripheral antinociceptive effects, \*\*\*In HHD, bacterial infection and inflammation potentiate acantholysis necessitating antibiotic and steroid applications. Gram-negative bacteria-derived lipopolysaccharide (LPS) and Gram-positive bacteria-derived lipotechoic acid (LTA) act as specific ligands for TLR4 and TLR2 signaling pathways, respectively, induce TLR4 activation that transactivates the production of proinflammatory cytokines. By inhibiting and reducing the expression of TLR4, ketamine significantly reduces the release of proinflammatory cytokines such as IL-6, IL-1, and TNF- $\alpha$

placebo – 4 mL of each cream was given for thrice-a-day application (12 mL/day) in patients with mixed neuropathic pain for 3 weeks. Of the 45 patients who received ketamine 1% or ketamine 1%–amitriptyline 2% combination cream, blood levels of ketamine at 3 weeks were detectable only in three patients (20–33 ng/mL) with none sustaining any systemic AEs.<sup>[13,15]</sup> The daily application amount in our report was lesser, and with the existing evidence of minimal to nil blood levels of ketamine on topical application of its 1% cream that too to a localized area, the likelihood of any significant blood absorption and systemic AEs is highly unlikely with topical ketamine 1%. In fact, reported clinically significant side effects are rare despite using higher concentrations of topical ketamine (5%–20%) with measured plasma levels of ketamine and norketamine (its metabolite) below the threshold of detection in various studies.<sup>[15]</sup> Akin to any topical ingredient, ketamine may have some potential for contact sensitization; however, it has not been reported in the studies conducted on topical ketamine till date. We still recommend that the DK cream preferably be used after patch testing by the patient.

In HHD, physical triggers and secondary bacterial infection induce and sustain acantholysis and inflammatory cascade. The antipruritic, antinociceptive, anesthetic, and anti-inflammatory effects of both the agents plus the bacteriostatic effect of diphenhydramine and naltrexone-mimicking effects of ketamine make DK cream an efficacious and safe agent for maintaining the therapeutic effect of LDN topically. We propose that DK cream may prove useful in HHD as an adjuvant to intermittent LDN treatment and for providing sustained maintenance of remission and low DLQI for at least few months even after discontinuation of LDN.

### Conclusion

This case not only adds on to the existing anecdotal evidence favoring the role of LDN in the management of HHD but also offers a topical regimen of diphenhydramine and ketamine to maintain the remission. Although the concentration of ketamine and the surface area of application were low, inability to measure blood levels of ketamine constitutes a major limitation. We recommend systematic exploration of this combination in studies with more patients with HHD.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not

be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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