Treatment of pruritus with topically applied opiate receptor antagonist

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Background: Pruritus is the most common and distressing skin symptom, and treatment of itch is a problem for thousands of people. The currently available therapies are not very effective. Therefore there is an urgent need to find new effective topical drugs against itching.

Objective: We conducted two separate studies to evaluate the efficacy of topically applied naltrexone, an opioid receptor antagonist, in the treatment of severe pruritus. The objective of the first open study was to correlate the clinical efficacy of topically applied naltrexone in different pruritic skin disorders to a change of epidermal μ-opiate receptor (MOR) expression. The second study was a double-blind, placebo-controlled, crossover study on pruritus in atopic dermatitis.

Methods: Initially we performed an open pilot study on 18 patients with different chronic pruritic disorders using a topical formulation of 1% naltrexone for 2 weeks. A punch biopsy was performed in 11 patients before and after the application of the naltrexone cream and the staining of epidermal MOR was measured. Subsequently, a randomized, placebo-controlled, crossover trial was performed with the same formulation. We included in this trial 40 patients with localized and generalized atopic dermatitis with severe pruritus.

Results: In the open study more than 70% of the patients using the 1% naltrexone cream experienced a significant reduction of pruritus. More interestingly, the topical treatment with naltrexone caused an increase of epidermal MOR staining. The regulation of the epidermal opioid receptor correlated with the clinical assessment. The placebo-controlled, crossover trial demonstrated clearly that the cream containing naltrexone had an overall 29.4% better effect compared with placebo. The formulation containing naltrexone required a median of 46 minutes to reduce the itch symptoms to 50%; the placebo, 74 minutes.

Limitations: We could only take biopsy specimens in 11 patients, which means that a satisfactory statistical analysis of the changes of epidermal MOR staining was not possible. In addition, there was an insufficient number of patients with nephrogenic pruritus and pruritic psoriasis to draw definitive conclusions.

Conclusions: The placebo-controlled study showed a significant advantage of topically applied naltrexone over the placebo formulation. This finding is supported by the biopsy results from the open studies, showing a regulation of MOR expression in epidermis after treatment with topical naltrexone, especially in atopic dermatitis. These results clearly show potential for topically applied opioid receptor antagonist in the treatment of pruritus. The placebo formulation also had some antipruritic effects. This underlines the importance of rehydration therapy for dry skin in the treatment of pruritus. (J Am Acad Dermatol 2007;56:979-88.)

Pruritus or itch is defined as an unpleasant subjective sensation associated with the desire to scratch. Pruritus induces a mechanical defense reaction, including pressing, rubbing, or scratching. The scratching leads to new irritation of the skin and this in turn induces pruritus, which

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Abbreviations used:

CNS: central nervous system
FAS: full analysis set
MOR: μ-opioid receptor
PP: per protocol
SPID: sum of the pruritus intensity difference
VAS: visual analogue scale

creates a vicious circle.[1] Pruritus is the most common and distressing skin symptom. The treatment of itch is a problem for thousands of people and is important not only for dermatology but also for all other medical specialties. The currently available topically applied drugs for pruritus, such as the antihistamines or polidocanol, are restricted by their limited efficacy when used by this route of administration and by their ability to sensitize. In addition, most patients with chronic pruritus do not respond to systemic treatment with antihistamines or steroids. Therefore there is an urgent need to find new effective drugs against itching.

For many years it has been suggested that the itch sensation is related to pain, and, indeed, the opioid peptides can influence the pain and itch sensation in a reversed way. Pruritus is a well-known and hard-to-control side effect of treatment with opioids for pain relief.[2] On the other hand, opioid-receptor antagonists, such as naltrexone and naloxone, have been used to treat different forms of chronic pruritus.[3-5] There have been several double-blind, placebo-controlled studies proving the effect of systemically applied naltrexone and naloxone in hepatogenic pruritus.[6-8] In addition, plasma from patients who have pruritus associated with chronic cholestasis induced opioid receptor–mediated scratching in monkeys,[9] and naltrexone treatment of this pruritus in humans precipitated an opioid withdrawal-like reaction.[10] These observations suggest a crucial role of the opioid receptor system and its ligands, such as β-endorphin, in chronic cholestatic pruritus. Systemically applied naltrexone reduced itching not only in patients with hepatogenic pruritus, but also in those with different pruritic skin diseases, such as atopic dermatitis, xerosis cutis, cutaneous lymphoma, and prurigo nodularis.[4] However, systemic naltrexone seemed to have no significant effect against uremic pruritus in a double-blind, placebo-controlled study.[11]

There is still an ongoing discussion as to whether this elicitation of itch is due to opioid receptors in the central nervous system (CNS) or in the peripheral nervous system. One of the most important indications that the opioid-induced pruritus is at least partially elicited in the periphery comes from the double-blind controlled studies with the opioid receptor antagonist methylnaltrexone. Methylnaltrexone, a novel quaternary derivative of naltrexone that does not cross the blood-brain barrier, acts as a selective peripheral opioid receptor antagonist and decreases pruritus and constipation, but still has an adequate maintenance of pain control.[2,12] This indicates that pruritus is elicited in the peripheral nervous system and modified in the CNS. Therefore we wanted to study the effect of a topically applied opioid-receptor antagonist against different forms of pruritus.

METHODS

Study objectives and design

Open pilot study. The main objective of this study was to see whether the topical application of the opioid-receptor antagonist naltrexone has an antipruritic effect and whether there is an objective effect, as studied by immunohistology. Therefore in two study centers we treated 18 patients with different pruritic disorders with a cream containing 1% naltrexone to see which kind of pruritus responds better to this treatment. The patients had to apply the study cream at the itching locations at least twice a day. The general intensity of the pruritus was measured by using a visual analogue scale (VAS) from 1 to 100 mm and the patients had to record the intensity of pruritus in their diaries in the morning, at noon, and in the evening. In addition, after 8 and 15 days the patient had to assess, together with the physician, the overall changes of pruritus. The clinical efficacy was judged according to the changes of the scratching intensity in the VAS as noted in the diary compared with day 0 (start of study). Additionally, in 11 patients we carried out a punch biopsy at the site of intense itching before and after the local treatment with the opioid receptor antagonist. The epidermal expression of μ-opiate receptor (MOR) and the changes of epidermal nerve endings were observed and semiquantified by immunohistochemistry using confocal microscopy. This pilot study showed that the topically applied opioid receptor antagonist worked best on patients with chronic pruritus associated with atopic dermatitis and lichen simplex chronicus.

Placebo-controlled, crossover study. We planned a second multicenter, randomized, double-blind, placebo-controlled, crossover, phase II study on patients with atopic dermatitis. The goal of this study was to confirm in a double-blind study design that topically applied naltrexone indeed has an antipruritic effect in atopic dermatitis. The study took 4 to 6 weeks and included 40 patients with severe attacks of pruritus. The patients were required to visit the study center 4 times: