JDDG Journal of the German Society of Dermatology

DOI: 10.1111/j.1610-0387.2009.07213.x

Adjuvant topical therapy with a cannabinoid receptor agonist in facial postherpetic neuralgia

Ngoc Quan Phan[1], Dorothee Siepmann[1], Ingrid Gralow[2], Sonja Ständer[1]
(1) Competence Center for the Diagnosis and Treatment of Pruritus, Clinic and Polyclinic for Skin Diseases, University Hospital of Münster, Germany
(2) Outpatient Pain Therapy Department, Clinic and Polyclinic for Anesthesia and Surgical Intensive Care, University Hospital of Münster, Germany

JDDG; 2010 · 8:88–91 Submitted: 19.6.2009 | Accepted: 8.7.2009

Keywords
- pain
- pruritus
- nociception
- palmitoylethanolamine
- zoster

Summary
Background: Postherpetic neuralgia is a frequent adverse event in herpes zoster patients and difficult to treat. Conventional analgetic therapy often fails to reduce the burning pain transmitted by unmyelinated nerve fibers. These nerves express cannabinoid receptors which exert a role in modulation of nociceptive symptoms. Therefore, topical therapy with cannabinoid receptor agonist seems likely to suppress local burning pain.
Patients and methods: In an open-labeled trial, 8 patients with facial postherpetic neuralgia received a cream containing the cannabinoid receptor agonist N-palmitoylethanolamine. The course of symptoms was scored with the visual analog scale.
Results: 5 of 8 patients (62.5 %) experienced a mean pain reduction of 87.8 %. Therapy was tolerated by all patients. No unpleasant sensations or adverse events occurred.
Conclusions: Topical cannabinoid receptor agonists are an effective and well-tolerated adjuvant therapy option in postherpetic neuralgia.

Introduction
Postherpetic neuralgia (PHN) is a common, difficult-to-treat adverse event that can occur in patients with herpes zoster [1]. A standardized definition of the disorder is still lacking; most commonly it is classified by duration. More recent studies have distinguished three phases: acute (neuralgia up to 30 days after the onset of initial skin changes), subacute (up to 120 days) and chronic postherpetic neuralgia (minimum of 4 months) [1]. As yet no validated data are available on the prevalence and incidence of this disorder. PHN affects an estimated 10–15 % of patients with herpes zoster [2]. The risk is much higher in patients with immune deficiency and rises with increasing age. 50 % of patients over age 60 have PHN, and among 70–80-year-olds that figure is up to 70 %.

Postherpetic neuralgia results from damage to the affected spinal ganglion and peripheral nerve tissue, including myelinated and unmyelinated sensory cutaneous nerves, caused by inflammation during the initial phase of herpes zoster, leading to neuropathic pain and sensory disturbances [3, 4]. Unmyelinated cutaneous C fibers mediate burning and dull pain as well as pruritus [5, 6]. This explains why 30–48 % of patients with PHN also report pruritus in addition to pain [7]. Analgesic therapy of PHN varies according to pain severity and consists of stepwise non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, carbamazepine, gabapentin, and pregabalin [8, 9]. Randomized controlled clinical studies are available on the use of topical analgesic therapy with lidocaine 5 % and capsaicin [10–12]. Because of insufficient data on the use of topical lidocaine in postherpetic neuralgia, it has not been recommended as a first-line therapy [10]. Use of capsaicin is limited in facial involvement, due to related side effects (burning) and the close proximity to sensitive areas (eyes, mucous membranes). The aim of this observational study was to investigate the analgesic efficacy of adjuvant therapy with a topical cannabinoid receptor agonist in PHN patients with facial involvement.

Table 1: Postherpetic neuralgia: Location, duration and quality of symptoms.

Acute neuralgia (up to 30 days after herpes zoster)						
Patient	**Age (years)**	**Location**	**Quality**	**History of PHN at baseline**	**Systemic analgesia**	**Length of therapy / response (based on VAS)**
1	48	T* I right	Dull pain, pruritus	1 week	none	2 weeks/100 %
2	49	T* I–III right	Stinging, burning, pruritus	1 week	Tramadol	4 weeks/100 %
3	81	T* I left	Pain under pressure	2 weeks	none	2 weeks/80 %
4	52	T* II right	Stinging, burning	4 weeks	Paracetamol	2 weeks/66.7 %
Chronic neuralgia (4 months or longer after herpes zoster)						
5	79	T* I right	Dull pain, pruritus	10 months	none	2 weeks/0 %
6	67	T* I left	Burning, pruritus	17 months	Gabapentin	4 weeks/88.9 %
7	66	T* I right	Dull pain, pruritus	26 months	none	2 weeks/0 %
8	79	T* I left	Stinging, burning pruritus	14 years	none	4 weeks/16.7 %

*Trigeminus.

Patients and methods

In this open observational study, 8 patients (2 women, 6 men; 48–81 years old, mean 65 years) with acute (PHN up to 30 days after initial skin changes; n = 4) or chronic (PHN for at least 4 months after initial skin changes; n = 4) postherpetic neuralgia after herpes zoster affecting the face (trigeminal nerve divisions: V1, n = 6; V2, n = 1; V1-3, n = 1) received a cream containing the cannabinoid receptor agonist N-palmitoylethanolamine (PEA, Physiogel AI Creme®) (Table 1). The cream was applied to the affected site twice daily for two to four weeks. Before and after therapy, a thorough clinical examination was performed with documentation of symptom intensity using a visual analog scale (VAS) from 0 to 10 (0: no pain, 10: worst pain imaginable). The study received approval from the ethics commission of the medical association "Ärztekammer Westfalen Lippe" and the Medical School of the University of Münster in Germany.

Results

Prior to application of the PEA cream, patients reported neuropathic pain (dull pain, stinging, burning) and in some instances (n = 6) pruritus of an average intensity of 4.1 on the visual analog scale. Symptoms had been present for between one week and 14 years. Three patients reported continued pain despite systemic analgesic therapy (paracetamol, n = 1; tramadol, n = 1; gabapentin, n = 1). In 5 of 8 patients (62.5 %) there was a marked reduction in pain symptoms and pruritus (median VAS values before/after: 4.75/1.00; p = 0.008; Figure 1). On average there was a significant reduction in pain of 87.8 % in these patients. The best results were observed in patients with acute postherpetic neuralgia. Three patients (37.5 %) with chronic PHN had no or only a minimal response (0–17 % reduction) (Table 1). Therapy was well tolerated by all patients. No dysesthesia or contact eczema occurred.

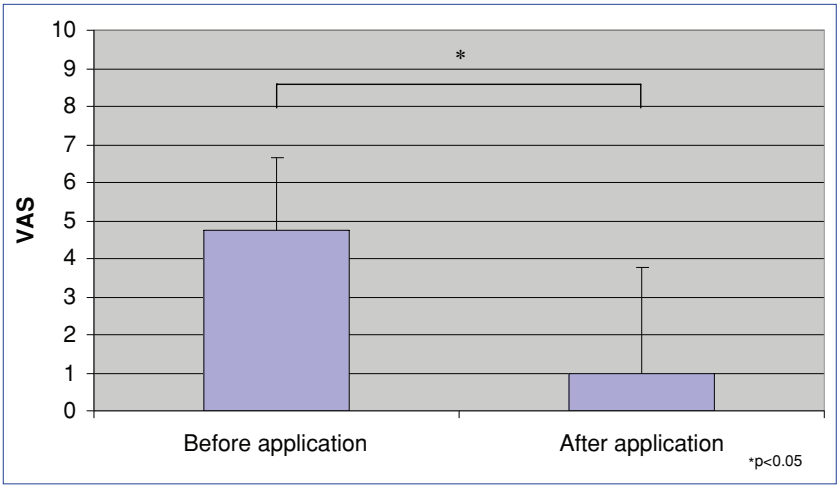

Figure 1: Symptom intensity (VAS) median before and after 2 to 4 weeks of therapy with the topical cannabinoid receptor agonist PEA.

Discussion

Palmitoylethanolamine (as well as other endogenous cannabinoids such as anandamide), are fatty acid ethanolamides which exert various anti-nociceptive and anti-inflammatory effects (e.g., reduced expression of NOS, COX-2, interleukin 1β, prostaglandin E_2) through their cannabinoid-receptors 1 (CB1) and CB2 as well as by activation of PPARα (peroxisome proliferator-activated receptor-alpha) [13–16]. PEA can also enhance the effects of other endocannabinoids at the respective receptor. In the skin, CB1 and CB2 are expressed on sensory nerve

endings, keratinocytes, and mast cells [14]. Both receptors play a role in modulating peripheral nociception, in particular inflammatory, thermal, and neuropathic pain [17, 18]. Experiments have shown that topical application of the synthetic CB1 and CB2 agonist "HU 210" can significantly suppress capsaicin-induced burning pain [19, 20]. Activation of CB1 has been shown to alleviate heat-induced hyperalgesia [21], while activation of CB2 reportedly reduces alloydynia in experimentally induced post-incision pain [22] and inflammatory hyperalgesia [17]. Animal models have confirmed additional analgesic effects on acute and chronic pain via activation of peripheral cannabinoid receptors [17]. The analgesic effect is possibly enhanced by cannabinoid-induced desensitization of the capsaicin receptor TRPV1 which is also found on cutaneous sensory nerve endings. Studies have shown that activation of cannabinoid receptors, and subsequent activation of the intracellular signaling cascade, leads to regulation of phosphorylation of TRPV1 [17]. In the epidermis, the activation of cannabinoid receptors causes endogenous opioids to be released from keratinocytes which contributes to pain reduction [23]. Peripheral stimulation of cannabinoid receptors has thus been suggested as a possible target in inflammatory and neuropathic pain therapies [17]. Previous studies reported an antipruritic effect associated with topical application of the cannabinoid agonist N-palmitoylethanolamine (PEA) in atopic dermatitis, nephrogenic pruritus, and prurigo nodularis [20, 24]. In the present case series, significant peripheral analgesic and antipruritic effects were seen in patients with acute postherpetic neuralgia. Patients with chronic postherpetic neuralgia had almost no reduction in symptoms, suggesting that extracutaneous, central processes related to chronic disease may contribute to pain which cannot be treated with topical therapies [25, 26].

Our results show that regular use of the topical cannabinoid receptor agonist PEA in acute postherpetic neuralgia can significantly reduce symptoms such as pain and pruritus. Especially in patients with facial involvement, topical application of PEA is an effective and well-tolerated adjuvant treatment option. <<<

Conflict of interest
Prof. Ständer received speakers' honoraria from the company Stiefel Laboratorium.

Correspondence to

Ngoc Quan Phan
Prof. Dr. med. Sonja Ständer
Kompetenzzentrum Pruritus
Klinik und Poliklinik für Hautkrankheiten
Universitätsklinikum Münster
Von-Esmarch-Straße 58
D-48149 Münster
Tel.: +49-251-83-56501
Fax: +49-251-83-52559
E-mail: sonja.staender@uni-muenster.de

References

1 Johnson RW, Whitton TL. Management of herpes zoster (shingles) and postherpetic neuralgia. Expert Opin Pharmacother 2004; 5: 551–9.
2 Rowbotham MC. Postherpetic neuralgia. Seminar in Neurology 1994; 14: 247–54.
3 Sorkin LS, Xiao WH, Wagner R, Myers RR. Tumour necrosis factor-alpha induces ectopic activity in nociceptive primary afferent fibres. Neuroscience 1997; 81: 255–62.
4 Baron R, Jänig W. Neuropathische Schmerzen. In: Zenz M, Jurna I: Lehrbuch der Schmerztherapie, Wiss. Verl.-Ges. Stuttgart, 2001: 475–84.
5 Ständer S, Schmelz M. Chronic itch and pain-similarities and differences. Eur J Pain 2006; 10: 473–8.
6 Ständer S, Steinhoff M, Schmelz M, Weisshaar E, Metze D, Luger T. Neurophysiology of pruritus: cutaneous elicitation of itch. Arch Dermatol 2003; 139: 1463–70.
7 Oaklander AL, Bowsher D, Galer B, Haanpää M, Jensen MP. Herpes zoster itch: preliminary epidemiologic data. J Pain 2003; 4: 338–43.
8 AWMF Leitlinie: Zoster und Zosterschmerzen. 2002. AWMF-Leitlinien-Register Nr. 013/023.
9 Wassilew SW. Zosterneuralgien. J Dtsch Dermatol Ges 2006; 4: 871–81.
10 Khaliq W, Alam S, Puri N. Topical lidocaine for the treatment of postherpetic neuralgia. Cochrane Database Syst Rev 2007; 18: CD004846.
11 Reimann S, Luger TA, Metze D. Topische Anwendung von Capsaicin in der Dermatologie zur Therapie von Juckreiz und Schmerz, Hautarzt 2000; 51: 164–72.
12 Watson CP, Tyler KL, Bickers DR, Millikan LE, Smith S, Coleman E. A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. Clin Ther 1993; 15: 510–26.
13 LoVerme J, La Rana G, Russo R, Calignano A, Piomelli D. The search for the palmioylethanolamide receptor. Life Sci 2005; 77: 1685–98.
14 Ständer S, Schmelz M, Metze D, Luger T, Rukwied R. Distribution of cannabinoid receptor 1 (CB1) and 2 (CB2) on sensory nerve fibers and adnexal structures in human skin. J Dermatol Sci 2005; 38: 177–88.
15 Richardson JD, Kilo S, Hargreaves KM. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. Pain 1998; 75: 111–9.
16 Calignano A, La Rana G, Giuffrida A, Piomelli D. Control of pain initiation by endogenous cannabinoids. Nature 1998; 394: 277–81.
17 Kress M, Kuner R. Mode of action of cannabinoids on nociceptive nerve endings. Exp Brain Res 2009; 196: 79–88.
18 Guindon J, LoVerme J, Piomelli D, Beaulieu P. The antinoceptive effects of local injections of propofol in rats are mediated in part by cannabinoid CB1 and CB2 receptors. Anesth Analg 2007; 104: 1563–9.
19 Rukwied R, Watkinson A, McGlone F, Dvorak M. Cannabinoid agonists attenuate capsaicin-induced responses in human skin. Pain 2003; 102: 283–88.
20 Dvorak M, Watkinson A, McGlone F, Rukwied R. Histamine-induced responses are attenuated by a cannabinoid receptor agonist in human skin. Inflamm Res 2003; 52: 238–45.
21 Johanek LM, Simone DA. Activation of peripheral cannabinoid receptors

attenuates cutaneous hyperalgesia produced by heat injury. Pain 2004; 109: 432–42.
22 LaBuda CJ, Koblish M, Little PJ. Cannabinoid CB2 receptor agonist activity in the hindpaw incision model of postoperative pain. Eur J Pharmacol 2005; 527: 172–4.
23 Ibrahim MM, Porreca F, Lai J, Albrecht PJ, Rice FL, Khodovra A, Davar G, Makriyannis A, Vanderah TW, Mata HP, Malan TP Jr. CB2 cannabinoid receptor activation produces antinoception by stimulating peripheral release of endogenous opioids. Proc Natl Acad Sci USA 2005; 102: 3093–8.
24 Ständer S, Reinhardt HW, Luger TA. Topische Cannabinoidagonisten. Eine effektive, neue Möglichkeit zur Behandlung von chronischem Pruritus. Hautarzt 2006; 57: 801–7.
25 Johnson RW, Wasner G, Saddier P, Baron R. Postherpetic neuralgia: epidemiology, pathophysiology and management. Expert Rev Neurother 2007; 7: 1581–95.
26 Harden RN. Chronic neuropathic pain. Mechanisms, diagnosis, and treatment. Neurologist 2005; 11: 111–22.