ISSN 2474-9206

Case Report

Journal of Anesthesia & Pain Medicine

Topical Phenytoin Cream Reduces Burning Pain Due to Small Fiber Neuropathy in Sarcoidosis

Jan M. Keppel Hesselink[1] and David J. Kopsky[2]

[1]*Institute for Neuropathic Pain, Spoorlaan 2a, 3735 MV, Bosch en Duin, The Netherlands.*

[2]*Institute for Neuropathic Pain, Vespuccistraat 64-III, 1056 SN, Amsterdam, The Netherlands.*

***Corresponding author**

David J. Kopsky, MD, Institute for Neuropathic Pain, Vespuccistraat 64-III, 1056 SN, Amsterdam, The Netherlands E-mail: info@neuropathie.nu.

Submitted: 03 June 2017; **Accepted**: 12 June 2017; **Published**: 28 June 2017

Summary

We present a patient case of burning pain and sleep disturbances due to small fiber neuropathy (SFN) in sarcoidosis, treated successfully by topically applied phenytoin 10% cream. Using a single blind, placebo-controlled response test, the patient identified that within a 10 minute period phenytoin 10% cream provided a pain reduction of 50%, while placebo cream did not reduce pain at all. Subsequently, the patient was prescribed phenytoin 10% cream and used this cream for several weeks. Burning pain was reduced by 50% to 60%, resulting in a much improved sleep. The onset of analgesia starts around five minutes after the application of phenytoin 10% cream and in this case lasts for around 20 hours. Plasma levels of phenytoin, measured in 15 comparable patients were below the level of detection, ruling out systemic analgesia. Our hypothesis is that topical phenytoin influences epidermal targets such as nociceptors, small nerve fibers and keratinocytes, all which play a role in the pathogenesis of pain in SFN.

Introduction

Burning pain as a symptom of small fiber neuropathy (SFN) is increasingly recognized as a medical problem, especially in the elderly and those patients suffering from diabetes. Symptoms of SFN typically start with burning feet and numb toes, and diabetes is in general regarded as the most common identifiable cause of SFN [1]. SFN and burning pain, however, can occur in many different disorders. It is known as a less frequent complication of sarcoidosis (Besnier-Boeck-Schaumann disease) [2]. We will present the study of a patient suffering from burning pain due to SFN in sarcoidosis who has been successfully treated by the application of phenytoin 10% cream.

In many cases of peripheral neuropathy, the impairment is mostly in small nerve fibers, and the clinical presentation consists of pain, burning, tingling, and numbness in a stocking-glove distribution [3]. Furthermore, small fibers are reported to be selectively damaged, especially in the early phases of diabetes [4]. Neurological examinations in patients suffering from SFN often reveal hyperalgesia, reduced vibratory sensation, pinprick and thermal sensation in the area where the patient experiences pain and numbness (paresthesia dolorosa). In most of the patients, nerve conduction studies and electromyography are normal.

Burning pain and associated symptoms, such as pins and needles, electric shock-like sensations and muscle cramps often are worse at night and disturb sleep, leading to exhaustion and less tolerability to the various pain sensations.

The impairment of the A-delta and C nociceptors, intra-epidermal situated structures, are related to the pathogenesis of burning pain in SFN and convey pain and thermal perception from the skin [5]. Currently there is no consensus on how to treat burning pain caused by SFN, and classical therapies such as tricyclic antidepressants, anticonvulsants and analgesic patches based on capsaicin or lidocaine are frequently prescribed. To date the Numbers Needed to Treat (NNT) for these therapies in SFN remain unclear and in general it is appreciated that analgesic therapy in SFN is a real challenge [6]. Below we will describe a case where burning pain has been treated successfully with phenytoin cream.

Case: SFN in sarcoidosis

For two years, a 62-year-old man has been suffering from stinging and burning pain in both lower legs and feet, 24 hours a day, and interfering with sleep. In this case, the pain was a complication of sarcoidosis diagnosed many years ago that was treated with various corticosteroid cycles. In addition, the patient had been feeling insecure while walking, and suffering from cramping sensations in both arms. His pain intensity score was registered as eight on the 11-point Numerical Rating Scale (NRS) scale, in which 0 is no pain and 10 is the most severe. His electromyography was normal, and the pregabalin 525 mg daily and oxycodone 10 mg as needed did not result in a significant analgesic effect. The patient was unable to tolerate higher doses of pregabalin. The SFN was supported by a neurological examination, a positive wrinkle test and a high score on the SFN questionnaire (score 51) [7].

An MRI of the brain was normal without signs of neurosarcoidosis. We administered single-blind phenytoin 10% cream on the right leg and placebo cream on the left. Within 10 minutes, the pain was reduced on the right side from a pain score of 7 to 4, while the pain on the left side did not change. The patient subsequently asked for the application of cream at the non-responsive side, and

within the same period of time the pain was reduced by around 50%. The patient stressed the fact that both legs felt much more at ease, and he also felt more stable while walking. Based on this positive response test we prescribed 10% phenytoin cream. Several weeks after the start of therapy the patient reported in general a reduction of pain between 50% and 60%. He gave his written consent to publish his experiences and added: "*The pain decreases in intensity after 5 to 10 minutes after application of the cream. The analgesic effect lasts for around 20 hours, and there is no need for additional applications. Sleep improved 60% to 70% in strong contrast with before, when I could not sleep and stayed awake for 4 to 5 nights a week. After rest in bed, previously, my whole left leg hurt a lot, but now, after the application of the cream, I can stay in bed. Furthermore, my stability is much better and I can also walk longer distances. The tingling is also significantly reduced*."

Discussion

The mechanism of action of phenytoin, concerning its analgesic effect when administered topically, has not yet been explored. This is due to the fact that up to recently it was unknown that topical phenytoin could reduce pain in a variety of neuropathic pain syndromes. Earlier we described several cases in which phenytoin alone or combined with other analgesics in a topical formulation could reduce neuropathic pain considerably [8-10]. Its mechanism of action, however, will be different from local anesthetics such as lidocaine, because patients do not report anesthetic effects after application of phenytoin formulations at the skin, while they do report such analgesic effects after the application of local lidocaine formulations and plasters [11].

Sodium channels are amongst the most important targets of phenytoin. Phenytoin stabilizes the inactivated state of the channel by effectively blocking the Na^+ conductance, while preventing synchronized high frequency firing, all leading to sensitization [12]. Some of these sodium channels can be found in the skin on the keratinocytes and the nociceptors. To date, only fragmentary insight exists in the role and the peripheral expression of sodium channels in pain-transducing free nerve endings in the skin and on the keratinocytes [13]. Sodium channels are reported in keratinocytes, $Na_v1.1$, $Na_v1.6$ and $Na_v1.8$. Immunolabeling is strong in epidermal keratinocytes. It was suggested that these channels could possibly contribute to pain. Pathological increases have been documented in keratinocyte sodium channel expressions found in the skin biopsies of patients suffering from neuropathic pain [13]. $Na_v1.6$, 1.7, 1.8, and 1.9 are also reported to be present in epidermal free nerve endings [14]. Our hypothesis is that the highly lipophilic anticonvulsant phenytoin formulated in a cream reduces pain via epidermal targets such as nociceptors and small nerve fibers as well as via keratinocytes. In order to rule out an analgesic effect via plasma, we tested a number of patients in our first series (n=15) and in all cases the plasma levels of phenytoin were below the detection limit.

Phenytoin cream in our case of SFN in sarcoidosis did not only substantially and during many hours reduce the burning neuropathic pain, but other symptoms also improved such as tingling, sleep and stability. Very recently it was documented that SFN can also affect stability in the absence of disturbances due to classical polyneuropathy. Early alterations in dynamics during walking were associated with small- but not large-fiber neuropathy in diabetes [15]. Ankle joint power during walking was reduced in SFN related to diabetes or impaired glucose tolerance. The improvement of stability and walking after the application of phenytoin 10% cream could be due to the fact that less distraction due to pain helps the patient to concentrate more on walking.

Of course, the analgesic effect reported by the patient could also be a placebo effect, however the fact that he responded positively on a single blind responder test reduces this chance. Future elegant single-subject designs will further reveal the analgesic effects of phenytoin cream.

Disclosure

The authors are holders of two patents: 1) topical phenytoin for use in the treatment of peripheral neuropathic pain and 2) topical pharmaceutical composition containing phenytoin and a (co-)analgesic for the treatment of chronic pain. The authors report no other conflicts of interest in this work.

References

1. Tavee J, Zhou L (2009) Small fiber neuropathy: A burning problem. Cleve Clin J Med 76: 297-305.
2. Bakkers M, Faber CG, Drent M, Hermans MC, Van Nes SI, et al. (2010) Pain and autonomic dysfunction in patients with sarcoidosis and small fibre neuropathy. J Neurol 257: 2086-2090.
3. Van Acker N, Rage M, Vermeirsch H, Schrijvers D, Nuydens R, et al. (2016) NRP-1 Receptor Expression Mismatch in Skin of Subjects with Experimental and Diabetic Small Fiber Neuropathy. PLoS One 11: e0161441.
4. Breiner A, Lovblom LE, Perkins BA, Bril V (2014) Does the prevailing hypothesis that small-fiber dysfunction precedes large-fiber dysfunction apply to type 1 diabetic patients? Diabetes Care 37: 1418-1424.
5. Kukidome D, Nishikawa T, Sato M, Igata M, Kawashima J, et al. (2016) Measurement of small fibre pain threshold values for the early detection of diabetic polyneuropathy. Diabet Med 33: 62-69.
6. Chan AC, Wilder-Smith EP (2016) Small fiber neuropathy: Getting bigger! Muscle Nerve 53: 671-682.
7. Treister R, Lodahl M, Lang M, Tworoger SS, Sawilowsky S, et al. (2017) Initial Development and Validation of a Patient-Reported Symptom Survey for Small-Fiber Polyneuropathy. J Pain 4: 014.
8. Kopsky DJ, Keppel Hesselink JM (2017) Topical phenytoin for the treatment of neuropathic pain. J Pain Res 10: 469-473.
9. Kopsky DJ, Keppel Hesselink JM (2017) Phenytoin in topical formulations augments pain reduction of other topically applied analgesics in the treatment of trigeminal neuralgia. Journal of Clinical Anesthesia 38: 154-155.
10. Keppel Hesselink JM, Kopsky DJ (2017) Phenytoin: a newly identified topical analgesic and its putative mechanisms of action: 2 case reports. J Pain Relief 6: 284.
11. Herberger K, Krause K, Maier K, Zschocke I, Radtke M, et al. (2012) Augustin M. Local anesthetic effects of Lidocaine cream: randomized controlled trial using a standardized prick pain. J Dermatolog Treat 23: 437-442.
12. Qiao X, Sun G, Clare JJ, Werkman TR, Wadman WJ (2014) Properties of human brain sodium channel alpha-subunits expressed in HEK293 cells and their modulation by carbamazepine, phenytoin and lamotrigine. Br J Pharmacol 171: 1054-1067.

13. McEntire DM, Kirkpatrick DR, Dueck NP, Kerfeld MJ, Smith TA, et al. (2016) Pain transduction: a pharmacologic perspective. Expert Rev Clin Pharmacol 9: 1069-1080.
14. Persson AK, Black JA, Gasser A, Cheng X, Fischer TZ, et al. (2010) Sodium-calcium exchanger and multiple sodium channel isoforms in intra-epidermal nerve terminals. Mol Pain 6: 1744-8069.
15. Almurdhi MM, Brown SJ, Bowling FL, Boulton AJ, Jeziorska M, et al. (2017) Altered walking strategy and increased unsteadiness in participants with impaired glucose tolerance and type 2 diabetes relates to small-fibre neuropathy but not vitamin D deficiency. Diabet Med 34: 839-845.