

Review

Small Fiber Burning Pain in Diabetic Neuropathy in The Elderly, Treated with Phenytoin Cream

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Abstract

Both idiopathic as well as secondary small fiber neuropathy (SFN) are characterized by a classical reduction of the intra epidermal nerve fiber density, and by a variety of different (differentiation) symptoms, such as burning pain, shooting pain, allodynia, and hyperesthesia. SFN is a major cause of painful burning sensations in the feet, especially in the elderly. Although neuropathic pain is more common in older persons rather than in younger, the majority of clinical trials have been conducted in younger adults. Based on such studies the general recommendation for the treatment of SFN pain is to start pharmacotherapy with gabapentinoids or tricyclic antidepressants such as amitriptyline. Elderly patients, however, are more susceptible to many side effects, and are also more likely to be affected by drug-drug interactions. We therefore need alternatives, with a better safety profile and less potency for drug-drug interactions. Treating pain by the administration of topical analgesics where the pain originates, in the epidermis at the level of the small fibers, may be a better option compared to oral pharmacotherapy. We present 2 cases of elderly patients who suffered from diabetic neuropathic pain with pain characteristics typical for SFN, and demonstrate the usefulness of topical phenytoin cream.

Introduction

There is consensus that small fiber neuropathy (SFN) leads to a variety of different (differentiation) symptoms, such as burning pain, shooting pain, allodynia, and hyperesthesia. There is also a consensus that SFN can be found in a variety of different diseases, from the metabolic syndrome and diabetes mellitus up to sarcoidosis and vitamin B12 deficiency. Around half of all patients with SFN, however, are diagnosed as 'idiopathic' after an extensive work-up [1]. SFN is increasingly being recognized as a major cause of painful burning sensations in the feet, especially in the elderly [2]. Burning feet are usually worse at night and disrupt sleep, lowering the patient's quality of life and compromising his/her condition. Elderly patients are especially vulnerable to such negative impact because oral neuropathic pain medication, such as oral amitriptyline, usually induces cognitive adverse events and may contribute to a further deterioration of

quality of life. Although chronic pain is more common in older persons than in younger, the majority of clinical trials have been conducted in younger adults [3]. Based on such studies, the general recommendation is to start pharmacotherapy with gabapentinoids or tricyclic antidepressants such as amitriptyline. Elderly patients, however, are more prone to interactions and side effects if these neuropathic pain medications are prescribed. We therefore need new alternatives. Treating pain topically where the pain originates, in the epidermis at the level of the small fibers, may be a better option compared to oral pharmacotherapy, leading too often to systemic toxic blood levels in the elderly.

Current topical treatments for neuropathic pain are lidocaine 5% patch and capsaicin 8% patch. Lidocaine inhibits voltage-gated sodium channels, and thus stabilizes the neuronal membrane potential of abnormally excitable peripheral nerve fibers [4]. The main disadvantage of patches is that its application on certain parts of the body can be complicated due to the shape, such as feet. The handling, therefore, can be complex, especially for elderly and thus the compliance can be suboptimal. Phenytoin is a broad acting voltage-gated sodium channel blocker, and has wound

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healing properties, thus suits very well for diabetic neuropathic pain as a topical analgesic, since wounds and ulcers are common comorbidities.

The diagnosis of SFN is a diagnosis per exclusion am, based on the history and physical examination, and on a skin biopsy evaluating the intra epidermal nerve fiber density to provide diagnostic confirmation. In the case of conduction disturbances, signs of disturbed large fibers, neuropathy of the large vessels may also be present. Diagnostic confirmation of SFN helps only by determining the proximal cause and leads to initiating causal therapy, for instance in diabetes mellitus. It does not help to select better analgesics. It is stipulated that new clinical studies specifically targeting pain in SFN, irrespective of its etiology, are necessary to support more optimized pharmacotherapeutical interventions [5].

The pathogenetic cause of burning pain, often felt in the skin or superficially under the skin, is most probably related to the increased firing of the remaining small fibers in the skin, comparable to differentiation hyperactivity. Many primary afferents become spontaneously active as a result of damage, which is one of the reasons why differentiation paradoxically causes pain. The discovery of the ectopic impulse generation in these small fibers was seen as an explanation as to why certain patients suffering from neuropathic pain find pain relief after treatment with membrane-stabilizing drugs [6]. This is one of the main reasons we believe that topical phenytoin can reduce burning pain due to SFN [7,8]. Phenytoin is a broad acting channel blocker, and sodium channels are overactive in small nerve fibers, keratinocytes and immune-modulatory cells.

Abnormal warm and cold sensation thresholds are suggestive for SFN, and patients suffering from burning pain in both feet with such abnormal thresholds will most probably have SFN. We present 2 patients with burning feet treated with phenytoin cream.

Case Presentations

We present 2 condensed descriptions of elderly patients suffering from neuropathic pain due to diabetes type 2, complaining of burning pains, and on examination with disrupted warmth cold discrimination with a score on the DN-4 (screenings questionnaire for neuropathic pain) above 4, and a pain score on the 11-point numerical rating scale (NRS) above 7. Both patients responded favorably with topically applied phenytoin 10% cream.

An 80-year-old male patient, suffering from diabetes mellitus type 2 since 2003, was treated with metformin 850 mg 3 times daily, tolbutamide 500 mg 4 times daily, 22 units long acting insulin daily, simvastatin and ezetrol. Apart from the diabetic neuropathy he had no further complications. He was previously treated with gabapentin without an adequate analgesic response. The DN-4 score was 6, which indicated that the pain was of neuropathic origin.

The main pain location was both feet, and the pain characteristics were burning, pins and needles, and painful cold especially during night.

The pain intensity was 8 on the NRS. We prescribed an analgesic cream: phenytoin 10% compounded in a base cream. The amount per application was 2 fingertip units, circa 1.2 grams. After application the pain was reduced to less than 3 on the NRS. The patient applied the cream twice daily. No side effects were reported. In order to exclude a systemic effect, we assessed phenytoin concentration in plasma after 14 days of application, at circa 3 hours after last application: the phenytoin plasma level was below the limit of detection.

A 60-year-old female patient, since 2012 suffering neuropathic pain due to diabetes mellitus type 2 stopped her previous analgesic (i.e. duloxetine) due to the absence of therapeutic effect, although a side effect was a gain of 30 kilos since the treatment commenced. Her former medication, metformin 850 mg once daily, was stopped in October 2017 because her HbA1c was very good: 4.3 mmol/L. The pain characteristics as described by the patient were burning, electric shocks, tingling, pins and needles, itchiness and numbness in the same area. Besides the neuropathic pain she complained of impaired balance when walking. On physical examination there was hypoesthesia for touch and pin prick, allodynia for soft stroking, disrupted warmth cold discrimination in both forefeet, and absent ankle jerk reflexes. The DN-4 score was 9.

Her pain score was 10 on the NRS. Phenytoin 5% cream was first prescribed. The amount per application was 1 fingertip unit. The onset of action was 15 minutes and the pain after application was reduced from 10 to 6 on the NRS. The duration of analgesic effect was 4 hours, and the patient applied the cream 3 to 4 times daily. The duration of use was since 6th January 2017 ongoing, with no side effects reported.

In a single-blind response test on 4th January 2017, the patient experienced pain reduction in the right foot after application of phenytoin 5% cream. The patient experienced no effect after application of baclofen 5% cream on the left foot. On 26th September 2017, the patient received phenytoin 10% cream. She subsequently reported that she felt very well. The pain intensity was reduced from 10 to 2 on the NRS with a duration of analgesia of 6 hours, and she applied the cream 3 times daily. The onset of action of phenytoin 10% cream remained at 15 minutes.

Discussion

We presented two elderly diabetic patients who suffered from burning pain and with disturbed warmth cold discrimination. Both were refractory to treatments with antidepressants or gabapentinoids. For such patients, alternative treatment modalities such as topical administered phenytoin cream may present a new solution. Phenytoin cream has been documented by us to treat burning pain in SFN fast and easily [9]. Phenytoin in the correctly selected pharmaceutical base most probably reaches the intradermal targets, the sodium channels on the various cell types in the epidermis and the nociceptors, and does not act via central mechanisms as the plasma levels after application are below the limit of detection [10].

This rules out the emergence of systemic side effects, in line with the absence of such side effects in the cases presented here. One extra advantage of the application of topical phenytoin cream is the fact that many elderly diabetic patients suffer from small skin lesions and phenytoin has a long track record of being safe using in wounds, and even wound healing properties are repeatedly proven [11]. Therefore, applying the cream on a non-intact skin seems not to be contra-indicated in contrast to other topical analgesics.

Phenytoin cream seems to be a rational choice for the treatment of neuropathic pain in idiopathic and symptomatic SFN. In the elderly especially this alternative needs further attention. A single-blind study in 20 patients has just been completed, supporting the efficacy of 10% phenytoin cream. We are currently preparing phase IIb/phase III randomized clinical trials to further evaluate phenytoin in the treatment of neuropathic pain.

Conflict of Interest

Authors are patent holders of two patents related to the topical formulations of phenytoin in the treatment of pain: 1) Topical phenytoin for the 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.

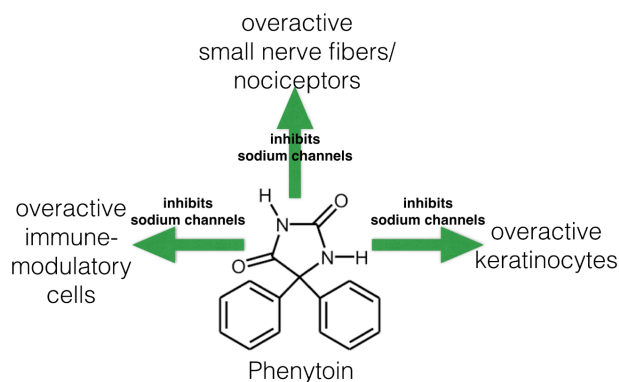


Figure 1. Phenytoin is a broad acting channel blocker, and sodium channels are overactive in small nerve fibers, keratinocytes and immunomodulatory cells in SFN.

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