Journal of Clinical Anesthesia and Pain Medicine

Research Article

Burning Pain in Small Fibre Neuropathy Treated with Topical Phenytoin: Rationale and Case Presentations

This article was published in the following Scient Open Access Journal:
Journal of Clinical Anethesia and Pain Medicine
Received February 12, 2017; **Accepted** March 10, 2017; **Published** March 17, 2017

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Abstract

This is the first presentation of a number of patients suffering from burning pain related to small fibre neuropathy (SFN), treated successfully with a topical formulation of the sodium channel blocker phenytoin. We present and discuss four patients complaining of severe burning pain, indicative for SFN, and its treatment with topical phenytoin. Burning pain and SFN occur amongst others in chronic idiopathic axonal neuropathy, chemotherapy induced neuropathy and in diabetic neuropathy, and we present for each indication an illustrative case. Burning pain also occurs in idiopathic small fibre neuropathy, and we present separately two patients to illustrate the use of our single blind response test for SFN in order to correct for possible placebo-effects. In all cases the burning pain could be relieved by topical phenytoin cream.

Burning pain has been related to mutations of the $Na_v1.7$ channel and this channel is one of the targets for phenytoin. In addition phenytoin can also block other sodium and calcium channels. Furthermore, phenytoin downregulates inflammatory cytokines in the skin, of which the production is enhanced in SFN and phenytoin has neuroprotective properties. We formulated a special topical cream, which enabled us to administer phenytoin in high concentrations (5% and 10%), leading to a fast and clinical relevant reduction of burning pain, without local or systemic adverse events. Based on these preliminary positive findings, a dose-finding phase IIb study is under preparation.

Keywords: Dilantin, Cream, Neuropathic, CIAP, Nav1.7, Analgesic, Local, Topiceutical, SFN

Introduction

Neural small fibre dysfunction can occur both together with large fibre neuropathy, such as in diabetic neuropathy, chronic idiopathic axonal polyneuropathy. (CIAP) and chemotherapy-induced peripheral neuropathy (CIPN), and it can also occur in isolated (idiopathic) forms [1-5]. Even in entrapment neuropathy syndromes, a clear reduction in intra-epidermal nerve fibre density is documented [6]. Recently, erythermalgia, prurigo nodularis, nummular eczema, burning mouth syndrome and sensitive skin were also classified as small fibre neuropathies [7]. The pathogenesis involved on the damage of small fibre remains unclear. The involvement clearly can be associated with many clinical conditions, which imposes a wide heterogeneity. Burning pain is a symptom often seen in small fibre neuropathy (SFN), reducing the quality of life considerably [8,9]. Diagnostic criteria however, are still in development [10]. Burning pain is regarded as one of the more severe symptoms of SFN and the pain often is persistent, but it may vary in intensity during the day [9]. Treatment of such pain is known to be difficult with the current pharmacological inventions [11]. Burning is also frequent in non-length dependent SFN or ganglionopathy [12].

The pathophysiology of burning pain, existing underneath the various and different manifestations of neuropathic pain syndromes, might be comparable and linked to the pathophysiology of burning pain in SFN. The reduction of intra-epidermal nerve fibre density is a key feature for the diagnosis of SFN. A number of SFN syndromes might be related to structural or functional disturbances of sodium channels, especially the $Na_v1.7$ channel, that are present within small peripheral nerve fibers [13]. A gain of function due to gene mutation of this channel has been described in 30% of patients suffering from SFN, causing hyperexitability [14]. Such findings contribute to the rationale, to treat patients with severe burning pain with topical analgesics that

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influence the $Na_v1.7$ channel and perhaps other sodium channels. One of these active compounds is the potent broad-acting sodium channel blocker phenytoin, we recently have developed and repurposed (repositioned) in a new topical formulation for a new indication. Phenytoin can directly influence both the primary nerve endings as well as other skin-elements contributing to the peripheral winding-up phenomena, such as the keratinocytes and the immune competent cells [15]. SFN therefore seems a viable option as a new indication for the repurposing of the old anticonvulsant phenytoin.

Phenytoin

A Remarkable Medicine Has Been Overlooked! is the title of a book written long ago by the billionaire John J. "Jack" Dreyfus, Sr. (August 28, 1913 – March 27, 2009). The topic of his book was the molecule phenytoin and its many putative indications. Dreyfus was the first to work out the repurposing profile of phenytoin in the 70s. Now, many years later, we discovered that topical phenytoin also can aid many patients suffering from painful conditions related to neuropathy. Neuropathic pain and burning in SFN are therefore new indications for phenytoin's repurposing as a patented analgesic cream.

Phenytoin is a versatile molecule, which has been discovered 80 years ago as an effective and safe antiepileptic, and was a great improvement over the bromides and barbiturates of that period of time. Since its first use in the clinic as an anticonvulsant drug, the efficacy of phenytoin has been evaluated in many different indications, from cancer to glaucoma [16-18]. Especially its neuroprotective properties have been highlighted since the last decades [19-22]. Phenytoin is a sodium channel blocker, amongst others with clear affinity and blocking properties for the $Na_v1.7$ channel [23]. The characteristics of phenytoin could be of great use in the treatment of SFN induced neuropathic pain, mainly based on four reasons (Figure 1). Firstly, phenytoin in our hands as a topical analgesic could reduce burning pain in a number of neuropathic pain states, via its sodium blocking properties. Secondly, phenytoin has a broad mechanism of action, blocking not only a series of sodium channels present in skin structures and nerve fibres, but also calcium channels and related targets. Thirdly, phenytoin downregulates the inflammation cascade and enhanced cytokine production in the skin, which has been documented to exist in SFN [24,25]. Finally, due to its neuroprotective properties phenytoin cream might be of use not only to dampen pain, but also to support nerve regeneration of small fibres. It has become quite clear that decreased intra-epidermal nerve fibre density can indeed be restored and improved via the influence of external factors [26].

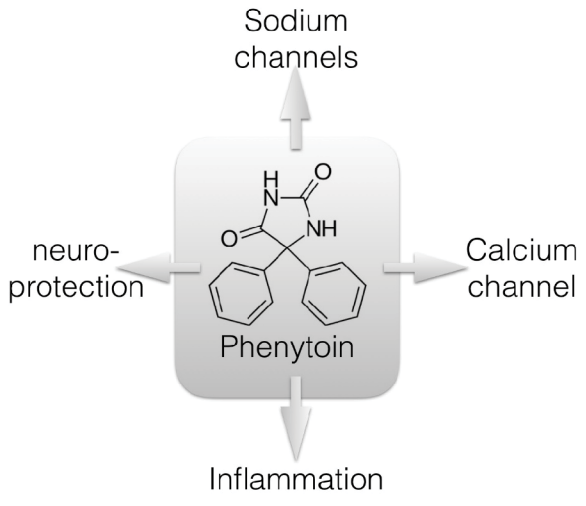

Figure 1: Mechanisms of action of phenytoin.

Case Presentations

A 74-year-old woman suffered burning CIAP pain in both feet since some years, and scored the pain with 6 on the 11-point numerical rating scale (NRS). The pain aggravated after walking. The patient did not tolerate pregabalin. Treating the patient with amitriptyline 10% cream, baclofen 5% cream, and lidocaine 3% combined with isosorbidedinitrate 0.4% cream did not give enough pain reduction. We than administered phenytoin 5% cream and this reduced the burning pain from 6 to 1 on the NRS, within 10 minutes after application. The duration of the effect was 5 hours. Subsequently, the patient applied the cream 3 times daily.

A 48-year-old man, with acute leukemia was treated with mitroxantrone and etoposide, and due to the chemotherapy a hand-foot syndrome started (redness and edema), and burning neuropathic pain in the feet. He scored the pain with an 8.5 on the NRS. Amitriptyline 10% cream reduced the pain considerably, scores on NRS decreased from 8.5 to 0, though unfortunately the effect lasted one hour only. Hereafter, prescribed additionally phenytoin 5% cream. This resulted in a complete disappearance of the pain during 3-4 hours, with a fast onset of effect of 15 minutes after application.

A 61-year-old man, suffering since 2007 from diabetes mellitus type 2 was treated with metformin 500 mg three times daily. The patient had burning pain in both feet and scored the pain as an 8 on the NRS. His sleep quality was very much disrupted due to the neuropathic pain. Treatment started with phenytoin 5% cream, resulting for the first time since years in the total absence of pain during the night. The patient applied the cream 3 times in 24 hours for obtaining sufficient analgesia, and in this case analgesic effects started 1 hour after application. The cream reduced the pain with 50% to a mean value of 4 on the NRS. All patients did not experience signs of adverse events.

Single Blind Response Test in SFN patients

Since we tested the phenytoin cream in the clinical setting, all of our patients informed us of its nearly immediate action of onset after application, within a time-frame of 15 minutes. This provoked us to develop a single-blind response test with placebo cream and the active cream, in order to identify responders during their first visit to our clinic, and thus reduce the chances that patients would, after an initial placebo response of some weeks, end up as non-responders to the cream. This test is easy and takes only a minute to conduct. We first document the baseline NRS of pain and burning sensations of two area's we are going to test. If patients suffering from SFN complain of pain at different sites, we ask them to undress, so that they can administer both placebo cream and the active cream on at least two comparable areas (mostly both feet). They then receive a fingertip unit (0.5 gram)

cream or placebo cream to rub in, followed by the phenytoin cream, with the same instruction. After 10 minutes we evaluate the NRS for both sites. We define a responder as those signaling a difference of 30% pain reduction or 2 points reduction on the NRS between placebo and the active response. We report here two men with SFN, diagnosis confirmed by a neurologist, of 62 and 74 years old, experiencing burning pain, already 13 and 29 months, respectively. The older patient was diagnosed as idiopathic SFN by the treating neurologist, the younger one SFN related to sarcoidosis, based on symptomatology, a positive wrinkle test and a high score (51) on the SFN questionnaire [27]. The younger patient experienced burning pain in the left arm and leg (NRS 7), whereas the other patient experienced burning pain, especially in his upper legs and knees (NRS 4). The placebo cream and the phenytoin 10% cream was applied on different areas of SFN pain, in a single-blind fashion. Both patients reported after 10 minutes a reduction of pain where phenytoin cream was applied, from 7 to 4 on the NRS, and 4 to 2 on the NRS, respectively. Both patients did not feel any pain relief in the area where the placebo cream was applied. Since both patients had a net reduction of more than 30%, we prescribed the phenytoin 10% cream.

Discussion

These five patients experienced burning pain as one of the main symptoms of the neuropathic pain they suffered from. Burning pain related to SFN occur in a variety of neuropathic pain syndromes, and we presented cases of CIAP, CIPN and diabetic neuropathy, as well as cases of idiopathic SFN. In the latter cases the diagnose SFN was confirmed by a neurologist. In all cases the burning pain could be relieved by topical phenytoin 5% or 10% cream. As far as we know this is the first presentation of patients suffering from burning pain most probably related to SFN, treated successfully with a topical formulation with the sodium channel blocker phenytoin. Phenytoin has many interesting characteristics, and apart from the blocking of sodium channels, such as the $Na_v1.7$ channel, the compound has neuroprotective and neurorestaurative properties, and furthermore inhibits calcium channels, even when these are tetrodotoxin insensitive [28,29]. Targets such as the $Na_v1.7$ channel and related channels are currently explored by pharmaceutical leaders in this field, such as Merck, Pfizer and Xenon Pharmaceuticals [30]. Phenytoin as a potent multi-ion-channel blocker is highly suited for topical administration, because this route avoids the systemic side effects related to its broad pharmacological profile, while its multi-target effect on skin structures could greatly contribute to its efficacy.

In addition to these mechanisms there might be another mechanism of action, via the inhibition of inflammatory cascades seen in various inflammation models after administrating phenytoin [31]. For instance, phenytoin could attenuate 50% of the release of IL-1α, IL-1β, and TNF-α from stimulated microglia [32]. It also reduced tissue edema and inflammatory cell infiltration during wound healing [33]. In SFN elevated pro-inflammatory cytokine expression, signs of neurogenic inflammation, has been documented in the affected skin [34]. In neurogenic inflammation a massive increase in sodium channels has been documented in the keratinocytes ($Na_v1.1$, $Na_v1.2$, $Na_v1.5$, $Na_v1.6$, $Na_v1.7$and $Na_v1.8$) [35]. Moreover, we have pointed out that peripheral wind-up in neuropathic pain is based on cross-talk between epithelial cells (e.g. keratinocytes), nerve endings and immune competent cells [36]. By applying phenytoin on the skin, it might be that the cross-talk, leading to peripheral sensitization, is smothered. Such cream might also be of great use for helping differentiate ex-juvantibus between non-length-dependent small-fiber sensory neuropathy (NLD-SFSN) and somatization disorders, if burning pain occurs in non-classical areas, such as on the chest, or in proximal parts of the extremities [37].

Finally, in SFN signs of re-innervation has been described in a number of papers, as discussed above. This might be an extra mechanism of action of topical phenytoin, theoretically resulting in a faster regeneration of the intra-epidermal nerve fibres [38]. Intra-epidermal nerve fiber regeneration has been described also in patients suffering from diabetes after the use of a sodium channel antagonist [39].

However, whatever the pathophysiological explanation of burning pain might be, topical phenytoin cream could serve as a new therapeutic modality in the treatment of neuropathic pain. It is an example of the continuous repurposing of phenytoin as a versatile old drug, due to its multi-target profile. However, the described cases are related to different etiolpathogenetic forms of SFN, and the interpretation of these isolated cases cannot confirm the effectiveness of the cream; it would therefore be suggested to perform arandomized double-blind clinical trial.

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.

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