CASE REPORT

Topical Phenytoin in Painful Diabetic Neuropathy: Rationale to Select a Non-selective Sodium Channel Blocker

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ABSTRACT

A short case of a patient suffering from painful diabetic neuropathy is presented to illustrate why it makes sense to prescribe a non-selective sodium channel blocker as a (co-)analgesic in a compounded topical formulation. To date, we have documented more than 100 patients treated with a compounded cream containing phenytoin. The case described here was one of the first in our data collection and was treated with 5% phenytoin cream, resulting in a 50% reduction of neuropathic pain. We selected phenytoin for compounding in a topical vehicle due to its profile as a broad acting archetypical sodium channel blocker and based on its remarkable properties as a repositioned multi-purpose drug. Its broad mechanism of action through blocking many subtypes of sodium channels in the skin not only inhibits overactivity of nociceptors but also may inhibit cross-talk between keratinocytes, immune-competent cell, and the nociceptor. After application, plasma levels of phenytoin were below the threshold of detection, and to date, no systemic adverse events related to its non-selective profile have been seen. Phenytoin is, therefore, uniquely suited for compounding in a topical formulation to treat peripheral neuropathic pain.

Key words: Diphantoin, neuropathic, pain, treatment

INTRODUCTION

Since 2010 we have been interested in the development of compounded creams containing relative high dosages of (co-)analgesics such as amitriptyline, ketamine, baclofen, and clonidine.[1] In the Netherlands, as in other European countries, prescribing old drugs for unapproved indications (off-label use) is acceptable, just as it is to prescribe compounded formulations in individual cases.

In the past years, a compounded topical formulation containing phenytoin was developed to treat peripheral neuropathic pain (off-label use), especially painful diabetic neuropathy (PDN) and pain in small fiber neuropathy (SFN).[2-4] These indications were targeted first, while sodium channels at the nociceptors in the epidermal fibers most probably play a major role in the pathogenesis of burning pain in PDN and SFN.[5]

Phenytoin is positioned as the archetypical sodium channel blocker.[6] Phenytoin is the oldest broad acting sodium blocker in clinical medicine and was introduced in 1938 by two neurologists. It was a major step forward in the treatment of epilepsy.[7] Its pharmacological profile resembles carbamazepine, and both drugs have a comparable mechanism of action related to their sodium blocking properties. Carbamazepine was introduced in the clinic much later, in 1962, and recently we discovered that both drugs are probably comparable in efficacy in trigeminal neuralgia. Only market driven arguments pushed carbamazepine into the position of a gold standard.[8] In our hand's topical phenytoin resulted in the alleviation of pain in trigeminal neuralgia.[9] Phenytoin

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has a broad pallet of pharmacological actions, which may explain its use in many indications.[10] It is, therefore, one of the prototypes of a repositioned or repurposed drug.

We will present a short description of a patient suffering from PDN due to diabetes mellitus (DM) Type 2 and follow-up by giving our rationale to focus on the non-selective sodium blocker phenytoin as an active pharmaceutical ingredient (API) to repositioning/repurpose in a topical analgesic cream.

CASE REPORT

A 61-year-old male patient was seen in our center, presenting with a classical distal symmetrical polyneuropathy, based on DM Type 2; no further electromyography evaluation was thought to be necessary, in line with Dutch guidelines for polyneuropathy.[11] DM Type 2 treatment: Metformin 500 mg 3 times daily. Previous analgesic use: Carbamazepine 200 mg daily.

Main pain location of pain was in both feet, and pain characteristics were burning, electric, tingling, pins, and needles. The Douleur Neuropathique 4 score was 7, clearly indicating neuropathic pain.

The pain nutritional risk screening-score before application of phenytoin 5% cream was 8. The amount of cream prescribed per application was 1 fingertip unit, 0.6 g. Within 60 min after application, the pain was reduced with 50%, and pain score after application was 4. The duration of the analgesic effect was around 8–12 h and patient applied the cream daily, 2–3 times. The patient used the cream subsequently with good effects, and no adverse events were reported.

This was one of the first patients who was entered into our ongoing database of over 100 patients, all treated with phenytoin topical compounded cream. In the first patients, we were careful and thus prescribed a relative low concentration of phenytoin, 5%. Subsequently, after finding no troublesome and concentration-limiting adverse events, we increased the concentration. Most patients are treated with 10% phenytoin cream, and occasionally in partial responders, we prescribe 20% or even 30%, sometimes resulting in better responses and also without adverse events. Based on our data pool analysis patients treated with higher concentrations (10% and above) often report a fast onset of action - mostly within 30 min. We analyzed phenytoin levels in 16 patients, around 2–3 h after cream application. In none of the patients, levels were above the limit of detection.

Phnytoin: The selection of a broad acting sodium channel blocker as an optimal drug in compounded cream for the treatment if the peripheral neuropathic pain.

In our center for the treatment of neuropathic pain, we exclusively see patients suffering from such pain. Most patients are referred to us through pain specialists, or they find their way to us through our internet site. Many patients have been treated unsuccessfully in the past and are refractory to most analgesics, or do not tolerate the adverse events. To expand the treatment for such patients, we developed a new treatment algorithm and compounded topical creams play a central role.

We started compounding creams based on amitriptyline, ketamine, baclofen, and clonidine and soon concluded concentrations selected elsewhere were in the sub-optimal dose range. The use of low dose API's in topical formulations often resulted in inconclusive results reported in literature.[12] Therefore, we started compounding creams containing higher concentrations such as 10% ketamine and 10% amitriptyline.[13] To further improve on our results, we explored literature to find a more suited compound. Thus, we identified phenytoin, a lipophilic small molecule with analgesic properties, optimally suited to penetrate the epidermis and to exert its sodium channel blocking properties locally, where the nociceptors are situated, in the epidermis. To use a non-selective compound is, however, quite against mainstream thinking. In general, one pleads for high selectivity in the field of sodium blocking agents for the treatment of neuropathic pain.[14] Teva for instance currently develops a potent Nav1.7 blocker for the topical use as an ointment in neuropathic pain, codename TV-45070.[15] Such high selectivity for a topical applied blocker we think is not required and perhaps even not advisable if the plasma levels after application remain in the low concentration range. TV-45070 mechanism of action is thought to be intradermally, and the ointment is, therefore, not developed for optimization of the transdermal penetrating of the active ingredient. If that was the case, high selectivity would perhaps be useful, in order not to induce systemic adverse events.

In the epidermis, on the nociceptors, many subtypes of sodium channels are expressed, and we still are in the phase of exploring the exact function of all these channels, as we will demonstrate below.

To date, nine subtypes of sodium channel have been cloned and identified on mammalian cells. Six of those nine sodium channels, except Nav1.2, expressed in the central nervous system, Nav1.4 and Nav1.5, expressed in muscle, have been identified as playing a possible pathogenetic role related to neuropathic pain and are being expressed in adult dorsal root ganglion neurons (DRGs) and the nociceptors in the skin.[16]

Nav1.1 is expressed mostly in the large-diameter A-fiber DRG neurons but can also be found in small non-peptidergic nociceptive neurons.[17] Peripheral nerve lesion increases NaV1.3 expression in DRG neurons, and mechanical

allodynia is reduced after oral administration of the Nav1 blockers, mexiletine, and lamotrigine.[18]

Nav1.1, Nav1.3, Nav1.7, and Nav1.8 are all significantly elevated in DRG isolated from NF1± mice, a mutation in man leading to increased pain experiencing.[19]

Nav1.6 expression increases proximal to a nerve lesion site, and it might be transported to the peripheral terminals in neuropathic pain conditions.[20]

Quite interesting is the observation that microglia express Nav1.1, Nav1.5, and Nav1.6.[21] Phenytoin could inhibit the behavior of immune-stimulated microglia, by significantly attenuating the phagocytic activity of lipopolysaccharide-activated microglia and reduced interleukin 1 alpha (IL-1a), IL-1b, and tumor necrosis factor-a secretion with more than 50%. Especially Nav1.6, and not Nav1.5, plays an important role in the migration of microglia. In other immune-competent cells, such as T-lymphocytes, blockade of sodium channels is also significantly attenuating the migration of these cells.[22] Furthermore, administration of phenytoin to mice with experimental multiple sclerosis was shown to decrease significantly the loss of axons and inhibit inflammatory infiltrate within the spinal cord, further supporting the immune-modulatory role of phenytoin.[23] As in many peripheral neuropathic pain syndromes and especially in PDN peripheral inflammatory factors play a role in the pathogenesis of pain, this putative extra mechanism of action of phenytoin might be quite important.[24] Due to its lipophilic nature, and being a small molecule, phenytoin can penetrate easily in all epidermal tissue compartments and exert its action on a multitude of cells expressing various subtypes of sodium channels.

Nav1.7, Nav1.8, and Nav1.9 are mostly expressed on small nociceptive neurons in the DRGs, but recently it was emphasized that even for these quite extensively explored sodium channels not much is known about their expression and function in human neurons.[25]

Our insight into the expression of these six channels in epidermal nociceptors, therefore, is incomplete, and much of what we currently know, might become modified in the light of new findings. The fact that most sodium channels can be found on afferent fibers and nociceptors, together with recent findings of sodium channels in other epidermal structures, the keratinocytes and the immune-competent cells, cross-talking with each other and with the nociceptors, supports the use of a non-selective sodium channel blocker in compounded analgesic topical formulations [Figure 1].[26] One example of this cross-talk is based on findings of pathological increases in sodium channel expression on keratinocytes leading to increased epidermal adenosine triphosphate release, inducing excessive activation of P2X receptors on the nociceptors.[27]

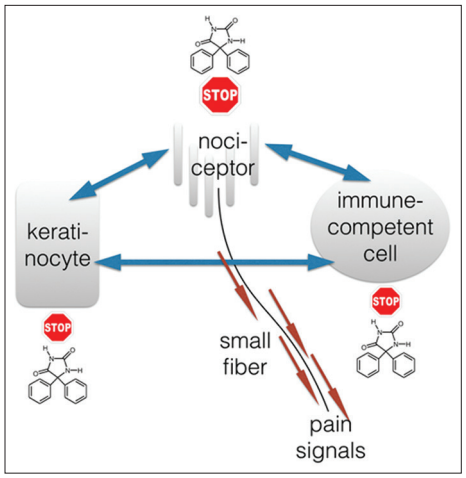

Figure 1: The crosstalk between the over-active nociceptor, keratinocyte and immune-competent cell, all containing sodium channels, can be inhibited by phenytoin, leading to analgesia and downregulation of peripheral sensitization, present in neuropathic pain

Phenytoin blocks a number of subtypes of sodium channels, due to the fact that its binding-site is situated at the inner cytoplasmic membrane, at the inner vestibule of the pore. This most probably explains its broad activity for nearly all sodium channels, as this binding site can be found in all members of this channel family.[28] Phenytoin forms interactions with the two aromatic rings of the two receptor residues and thus effectively blocks the pore.[29,30] Phenytoin, as well as carbamazepine, based on their tricyclic structure, interacting with the inner pore of the sodium channel, specifically in Domain IV and the S6 helix. The binding sites both tricyclic compounds have in common with local anesthetics are Phe-1764 and Tyr-1771. In addition to this, pharmacological data have emerged supporting phenytoin's affinity to sodium channels Nav1.1,[31] Nav1.3,[32] Nav1.5,[33,34] Nav1.6,[35] Nav1.7,[36] Nav1.8, and Nav1.9.[21] However, clearly not much modern pharmacology specifically looked into the binding of phenytoin to these various subtypes of channels in great detail. Given the studies into the pore-binding properties of phenytoin, it is quite clear this blocker can indeed be characterized as the archetypical sodium channel blocker.

CONCLUSION

Phenytoin can block sodium channels expressed on the nociceptor, the keratinocyte and immune-competent cells in the skin. Thus, it can inhibit both the overactive nociceptor, as well as the cross-talk between components in the epidermis with this nociceptor and potentially downregulate peripheral sensitization. We selected this archetypical sodium channel blocker to compound as a topical formulation for the treatment of peripheral neuropathic pain syndromes. Due to the fact that phenytoin seems not to penetrate into the blood, and its mechanism of action is located intraepidermal, we feel

the selection of this non-selective sodium channel blocker in a topical formulation is supported.

CONFLICT OF INTEREST

The author is one of the patent holders of two patents related to the repurposing of phenytoin: "Topical phenytoin for use in the treatment of peripheral neuropathic pain" and "topical pharmaceutical composition containing phenytoin and a (co-) analgesic for the treatment of chronic pain."

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