

Topical Phenytoin in Neuralgic Pain, Peripheral Modulation of Central Sensitization: Two Case Reports

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Abstract

We herewith describe a topical formulation of phenytoin with a clear analgesic effect in localized neuropathic pain: in post herpetic neuralgia and trigeminal neuralgia. Such topical analgesic effect for phenytoin has not yet been described in literature. We have developed various topical phenytoin formulations and identified a stable cream base in which we compounded a range of concentrations of phenytoin up to 10%. We will present two cases supporting the analgesic effect of phenytoin cream in neuralgic pain, and discuss the putative mechanism of action of phenytoin as a topical analgesic. The essence of both cases is that, apparently, it is possible to down-regulate central sensitization processes via the modulation (inhibition) of peripheral input. This hypothesis was brought forward in 2013 based on neurophysiological data, and our clinical data seem to also support this important chapter in pain treatment. Thus, topical analgesia, in our case based on phenytoin, can play an important role in multimodal therapy of chronic neuropathic pain, related to central sensitization states.

Keywords: Neuropathic pain; Phenytoin; Topical analgesic

Introduction

In 1908 phenytoin was synthesized for the first time and the introduction into the clinic as an anticonvulsant was many years later, in 1938. Although the molecule is a centenary, its mechanisms of actions are still not fully elucidated. Since the 80s of the last century the central mechanism of action of phenytoin is in general considered to be based on its blockage of the voltage gated sodium channels. The mechanism of action of phenytoin as an analgesic when administered via a topical formulation has not been explored and discussed yet. Its mechanism will be different from local anesthetics, because patients do not report the classical anesthetic effects after application, while they do report analgesic effects, with an action of onset between 3 to 30 minutes. Furthermore, there are clear differences documented between anesthetics and anticonvulsants related to biological read-outs [1]. In 2013 Baron and Dickenson published a seminal paper on the importance of peripheral modulation in chronic pain states characterized by central sensitization [2] They pointed out that both in the pathogenesis of chronic and neuropathic pain, as well as in the treatment, peripheral input is a neglected factor and presented neurophysiological evidence to illustrate that central sensitization read-outs are reduced after topical treatment with lidocaine. It is clear that this hypothesis opens a whole new chapter of the treatment of neuropathic pain. Clinical supportive data however have been absent. We will present two cases which support the hypothesis of Baron and Dickenson.

Case Descriptions

In our Institute for Neuropathic Pain (INP) we develop compounded creams for the treatment of neuropathic pain since 2011

[3-9]. In some of these cases presented, central neuropathic pain could be reduced by the application of a topical analgesic, which is quite contra-intuitive [3].

We have developed a base formulation, which is suited to deliver and combine a number of hydrophilic and lipophilic analgesics. Phenytoin is the father of all anticonvulsants, and its multipurpose profile in non-convulsive indications such as chronic pain was established in somewhat older studies. We identified that phenytoin in itself, topically administered, especially in the dose range of 5% to 10%, had good efficacy in the absence of troublesome side effects in a number of neuropathic pain states, as far as cases can support such conclusion. Topical phenytoin does not seem to create detectable plasma levels, as phenytoin formulations used in wound healing and applied in a dose of 100 to 200 mg daily on wounds did not result in measurable plasma levels [10,11]. Patients have not reported any systemic side effects during treatment with topical phenytoin 5% and subsequently with 10%.

We developed in our clinic a fast responder test, based on single blind application of either a fingertip unit placebo cream, or a fingertip unit phenytoin cream, applied on the painful region. Most patients can flawlessly identify the active cream within 10 minutes, and in cases of small fiber neuropathic pain we could document a 50% reduction of pain within this period of time. In a number of recent articles, we have presented the clinical effects of the phenytoin cream more extensively, here we especially want to embed the cases in a discussion on the mechanism of action of the cream.

Case 1: Phenytoin 5% cream for Trigeminal Neuralgia

An 86-year-old woman, suffered since years from severe trigeminal pain with burning and tingling sensations. Gamma-knife intervention, gabapentin, lidocaine 5% patch, and duloxetine did not have any effect.

Clonazepam 0.5 mg 3 times daily made life acceptable, though she scored her pain around the eye still with a 9 on the NRS. Ketamine 10% cream did reduce some of the sharp characteristics of the pain, but its effect was barely noticeable. However, ten minutes after application of phenytoin 10% cream the pain reduced from 9 to 5 on the NRS. She had to apply the cream frequently as the analgesic effect was lasting for one to several hours only. The burning and tingling sensations were reduced from 9-10 to 6-7 after applying the cream. The subjective feeling of stiffness around the mouth was reduced from 10 to 8.

Case 2: Phenytoin 10% for Post-herpetic Neuralgia

An 83-year-old man, suffering for 2 years from thoracic herpes zoster, scored his pain as 7 to 8 on the NRS, while using pregabalin 600 mg daily. Lidocaine cream, capsaicin 8% plaster, amitriptyline had no effect on his pain. Single blind treatment with 10% ketamine cream compared to phenytoin 10% cream demonstrated superiority of the phenytoin cream. The pain reduction of 50% emerged within 20 minutes after application, lasting for around 4-6 hours. Ketamine cream had only marginal effects, if any.

Mechanisms of Action

More than 17,000 articles on phenytoin can be found in PubMed. The peak number of research papers reached 477 in 1983. Since 1983 the number of papers published each year diminished, and slowly leveled out to around 300 papers each year since 2000.

Many mechanisms of action have been reported and discussed for phenytoin, in the beginning purely related to its anti-convulsive efficacy, but soon, after the first reports of gingiva hyperplasia as a side effect, also related to these effects and other emerging indications, such as wound healing. Phenytoin has been explored in many indications, and the most recent ones are breast cancer and optic neuritis [12-14].

The first study into the mechanism of action of phenytoin was published in 1937 [15]. Putman and Merritt described the effects of phenytoin in an animal model for seizures and documented that the compound could raise the threshold for electroshock induced convulsions [15]. Twenty years after its introduction, Bray hypothesized that the main mechanism of action of phenytoin related to its anticonvulsive effect was "to produce a shift from sodium from inside the brain to the extracellular space", and to increase the concentration of serotonin in brain tissue [16]. Discussions on the mechanism of action of phenytoin thus started in the first part of last century, but these were still quite speculative and general. Among the first mechanisms proposed in the second half of last century for phenytoin as an anticonvulsant are excitable membrane stabilization, decrease in post-tetanic potentiation, augmentation of presynaptic and postsynaptic inhibitions, and depression of synaptic transmission [17-22]. Clearly, these mechanisms of action were described at the level of biological effects in various neuronal tissues and not at the level of receptors. This changed in the 70s and 80s of the last century. From that time onwards it became clear that phenytoin inhibited sodium conductance in nerves via ion channels [20]. Later, in the 80s experiments with among other synaptosome-systems supported the idea that phenytoin blocked sodium channels [23-25]. This was the beginning of the emerging insight that phenytoin could selectively block voltage-gated sodium channels.

Voltage-gated sodium channels: A key target for phenytoin

Voltage-gated sodium channels (Nav) play a key role in cellular excitability in nerves, as well as in other tissue. There is a clear consensus that these 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. Phenytoin (IC₅₀=40 μm) has 6 times stronger sodium channel binding activity compared to lidocaine (IC₅₀=240 μm) [26]. This is especially relevant in the context of the Baron and Dickenson hypothesis of 2013, where lidocaine was documented to be able to downregulate central sensitization read-outs after topical application [2]. Data on specific effects of phenytoin, as compared to other anticonvulsants, related to the various sodium channels in various tissues are sparse or even absent [27]. Most of the voltage-gated sodium channels are expressed in parts of the central and peripheral nervous system. Anesthetics that block such channels need therefore to be administered topically or locally to avoid undesired, systemic side effects, such as with IV lidocaine. Sodium channels however, are also to be found in the skin, and especially on the keratinocytes [28]. It is here, that the inhibitory feedback from the periphery to the central nervous system, as hypothesized by Baron and Dickenson starts.

Since some years we understand there is a family of Nav and some of these are new targets for drug development. Currently we can differentiate between 9 Nav isoforms (Nav 1.1-1.9), all sharing significant homology. Moreover, the α-subunits of these channels seem to have different cellular and subcellular expression patterns which determine their different functional role, and phenytoin might play a unique role on this level. Nav 1.3, 1.7, 1.8, and 1.9 most probably are channels for nociceptive transduction. Sadly enough only fragmentary insight exists in the role and the peripheral expression of sodium channels in pain-transducing free nerve ending in the skin and on the keratinocytes [28]. The sodium channels, Nav1.1, Nav1.6 and Nav1.8 are abundantly present at epidermal keratinocytes [29]. These sodium channel have differential patterns of distribution within the epidermis. Labeled axons within the dermis were detected for Nav1.2, Nav1.7, Nav1.8 and Nav1.9, but its immunolabeling was much less intense compared to the keratinocytes. It was suggested that these channels could possibly contribute to pain [29]. Pathological increases have been documented in keratinocyte sodium channel expression found in skin biopsies of patients suffering from neuropathic pain [29]. Stimulation of the channel leads to increasing epidermal ATP release and triggers an excessive activation of P2X receptors on primary sensory neurons. Sodium channel immunolabeling and laminar distribution are increased in the epidermis of all painful complex regional pain syndrome (CRPS) skin biopsies [29]. Specifically, painful neuropathic sites in the skin had more intense immunolabeling for Nav1.2, Nav1.2, Nav1.5, Nav1.6, Nav1.7 and Nav1.8. These findings are strongly in support of topical treatment, and the authors concluded: "Epidermal signaling pathways merit further investigation as targets for peripherally acting analgesic drugs that lack CNS side effects" [29].

Nav1.6, Nav 1.7, Nav1.8, and Nav1.9 are also reported to be present in epidermal free nerve endings [30]. Phenytoin, dose-dependently inhibited Nav1.7 in a new activator paradigm which was presented as a possible probe to develop a rapid throughput screening assay to identify Nav1.7 antagonists [31].

Phenytoin could significantly inhibit ERK1/2 phosphorylation and at anti-convulsive concentrations (50 μm), phenytoin significantly

inhibited both persistent and transient Na⁺ currents in the de novo resistant breast cancer cells via blocking effects on the Nav1.5 channel.

As the major drug binding site of sodium channels is not accessible from the extracellular side, drug molecules can only access it either from the membrane phase, or from the intracellular environment [32].

Phenytoin most probably, due to its lipid nature, will at least partly enter the channel via the lipid membrane compartment. Phenytoin is expected to accumulate just inside the lipid head groups where they may alter bilayer properties or interact with their target [33]. Recent work on the bacterial voltage gated sodium channel made it likely that phenytoin has two binding sites in the pore, characterized by nonspecific, hydrophobic interactions [34]. Some clinical cases in rare forms of epilepsy, where children were good responders to treatment with phenytoin, support its effect on the overactive Nav1.6 channel [35].

Phenytoin also inhibits of calcium entry through voltage dependent L-type calcium channels [36]. Especially during excited states, for instance in neuronal models stimulated with picrotoxin, γ -aminobutyric acid (GABA) type A receptor (GABA_A) antagonist, phenytoin has a strong effect on the suppression of the spontaneous hyper-exciting excitatory postsynaptic currents [37].

By using modeling of neuronal networks, the differentiated effects of phenytoin were shown to be determined by the complexity of the network, as well by the heterogeneity of the components in this network [38].

Based on the above discussed findings, it is clear that phenytoin has a number of targets in the family of voltage gated sodium channels, and that these channels are distributed widely in the skin, on nociceptors and keratinocytes, having close communication. Both cell types furthermore are involved in intense cross-talk related to chronic pain and inflammation [39]. These mechanistic arguments together with the hypothesis put forward in 2013 on the relevance of modulation of peripheral input in neuropathic pain, support the analgesic effect of phenytoin in a number of neuropathic pain syndromes and neuralgia. Apart from the sodium channels, there are more systems in the periphery phenytoin could target, such as GABA receptors and NMDA receptors.

Potentiation of GABA

GABA and its receptor, a ligand-gated chloride ion channel reduce neuronal excitability in neurons. GABA most probably also plays a role in the physiology of keratinocytes, and is observed within the keratinocyte [40-42]. One of the enzymes involved in the synthesis of GABA has been identified in the skin [43]. We know that GABA_B receptors, are peripheral targets for analgesia with selective GABA_B agonists, such as baclofen [44]. Phenytoin in the 70s was already described as having GABA-ergic effects [18]. Moreover, neurophysiological read-outs show that phenytoin influences GABA_A and GABA_B [45]. The responses of neurons to GABA can be potentiated by phenytoin [46-48]. The affinity of phenytoin for the GABA_A receptor is in the nano molar range [49].

N-methyl-D-aspartate (NMDA) receptor antagonism

Expression of the NMDA receptor is altered in diseased skin containing tumor necrosis factor α (TNF α), and we can find this molecule in many states of chronic inflammation [50]. Increased keratinocyte proliferation and increased inflammatory mediators such

as TNF α have been found in a CRPS model [51,52]. Phenytoin attenuates α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated depolarizations by the agonists AMPA and quisqualate in mM concentration range, but is not able to fully antagonize responses to NMDA at concentrations less than 100 mM. Ionotropic glutamate receptors of the NMDA receptor type are expressed on keratinocytes [53,54]. Phenytoin could effectively decrease the synaptic excitation through influencing the NMDA receptor [45]. However, given the affinities for this receptor described for the central nervous system, these receptors most probably do not play a major role in the topical analgesia induced by phenytoin [55].

Other peripheral mechanisms of action

Effects of phenytoin on peripheral nervous system read-outs have been described since nearly half a century, based on a number of different studies and models [56-59]. Treatment in sciatic nerve rat and frog models with phenytoin, even at subclinical concentrations of 5 mg/ml, caused a significant decrement in the amplitude and increment in the latency of the compound action potential [1,60]. In a rabbit model of unmyelinated C fiber a reduction of conduction velocity was reported after intraperitoneal dosing with phenytoin, and this led to a decrease in post-titanic hyperpolarization [61]. Such data support a possible mode of action via peripheral nerves, and might contribute to the analgesic effects of phenytoin after application on the skin, and strengthen even more the hypothesis of Baron and Dickenson.

Influence of phenytoin on skin cells

There are many different tissues in the skin, and as we discussed elsewhere, skin offers a multitude of targets for topical analgesia: nerve endings, keratinocytes and immune competent cells. In addition to these targets all three elements are involved in intense cross-talk [62]. We will only shortly highlight some of phenytoin's impact on skin cells. The effects of phenytoin on the keratinocytes in the skin have been outlined above in the chapter of sodium channels. Here we will describe some of phenytoin's other actions on skin level. In 1939 gingiva hyperplasia was reported after phenytoin treatment [63].

The first suggestion phenytoin could play a supporting role in healing wounds was done by Shapiro in 1958, based on its accelerated epithelialization and increased connective tissue activity [64]. One year later the first results were published documenting wound healing properties of phenytoin in a controlled clinical trial [65]. The mechanism by which phenytoin improves wound healing however, is still not identified, neither is the most optimal way of delivering topical phenytoin [11].

Phenytoin is metabolized in the skin and it was pointed out that gingiva showed significant phenytoin hydroxyls [66]. Both cytochrome P450-dependent monooxygenase and epoxide hydrolase are documented in gingiva and human skin, and thus it was suggested that gingiva and skin might be important extra hepatic sites for the metabolism of phenytoin. From a number of experiments it also became clear that phenytoin has multiple direct and indirect actions on various tissues in skin and gingiva [66]. Some of these hitherto unknown mechanisms might also play a role in the anti-nociceptive effects of topical phenytoin we found in neuropathic pain.

Conclusion

Eighty years after the first clinical use of phenytoin, new indications and new mechanisms of action keep being identified. We discovered

the analgesic activity of a topical formulation of phenytoin in localized neuropathic pain, such as post-herpetic neuralgia and trigeminal neuralgia. Our cases support the hypothesis of Baron and Dickenson put forward in 2013, that in multimodal pain therapy one should also downregulate peripheral input, even in pain states with clear central sensitization. There are a multitude of targets in the skin for understanding these peripheral analgesic mechanisms of action of phenytoin in a topical formulations, such as in creams. Both keratinocytes as well as nerve endings in the skin can serve as targets for phenytoin, and both structures carry various voltage gated sodium channels. However, there may be other, hitherto unidentified targets for phenytoin in skin structures. Phenytoin, due to its lipophilic nature, seems quite attractive as a topical agent in the treatment of neuropathic pain, especially since a number of targets relevant for the treatment of neuropathic pain reside in the various components of skin, such as keratinocytes and the nerve endings of the nociceptors.

Conflict of Interest

Both authors are patent holders of two patents related to topical phenytoin formulations.

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