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CASE SERIES

Topical phenytoin for the treatment of neuropathic pain

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Abstract: We developed and tested a new putative analgesic cream, based on the anticonvulsant phenytoin in patients suffering from treatment refractory neuropathic pain. The use of commercial topical analgesics is not widespread due to the facts that capsaicin creams or patches can give rise to side effects, such as burning, and analgesic patches (e.g., lidocaine 5% patches) have complex handling, especially for geriatric patients. Only in a few countries, compounded creams based on tricyclic antidepressants or other (co-)analgesics are available. Such topical analgesic creams, however, are easy to administer and have a low propensity for inducing side effects. We, therefore, developed a new topical cream based on 5% and 10% phenytoin and described three successfully treated patients suffering from neuropathic pain. All patients were refractory to a number of other analgesics. In all patients, phenytoin cream was effective in reducing pain completely, without any side effects, and the tolerability was excellent. The onset of action of the phenytoin creams was within 30 minutes. Phenytoin cream might become a new treatment modality of the treatment of neuropathic pain.

Keywords: phenytoin, topical administration, neuropathic pain, diabetic neuropathy, chemotherapy-induced polyneuropathy, analgesia, drug repositioning

Introduction

Neuropathic pain can be debilitating and reduces quality of life considerably.[1,2] Peripheral neuropathic pain has a local inflammatory component, which results in sensitization of peripheral nerve fibers.[3] Damage and metabolic stress of the nerves result in increased production of pro-inflammatory mediators (e.g., cytokines and interleukins) in both peripheral and central neurons and nonneuronal cells, such as Schwann cells, mast cells, and glia cells.[3] These pro-inflammatory mediators sensitize nerve fibers and nociceptors, leading to clinical symptoms of neuropathic pain, such as burning, tingling, pins and needles, painful cold, electric shock, itch, hyperalgesia, and allodynia.

Peripheral nerve damage and increased peripheral input result in enhanced neurotransmitter release within the spinal cord and contribute to the process and maintenance of central sensitization, and thus neuropathic pain.[4] Peripherally acting drugs, such as lidocaine, formulated in topical creams or as patches, have demonstrated the ability to reduce central sensitization through blocking the peripheral input.[4,5]

Oral antidepressants (e.g., amitriptyline and duloxetine) and anticonvulsants (e.g., pregabalin and gabapentin) are the first-line treatments for neuropathic pain; tramadol and strong opioids (e.g., oxycodon) are second- and third-line treatments, respectively.[6] However, the majority of patients is not compliant, most probably because of

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the absence of expected effects or the induction of intolerable side effects, including sedation, dizziness, depression, nausea, and constipation.[7] Furthermore, the chronic use of such analgesics can induce drug–drug interactions as well as nephrotoxicity and hepatotoxicity. Unfortunately, despite partial pain relief through standard treatments, neuropathic pain may get worse overtime. New treatments, preferably devoid of troublesome side effects and drug–drug interactions are, therefore, required. Topical analgesics might contribute to this field.[5]

Two commonly used topical analgesics are lidocaine (a voltage-gated sodium channel blocker) and capsaicin (a vanilloid receptor agonist).

Lidocaine inhibits voltage-gated sodium channels, and thus stabilizes the neuronal membrane potential of abnormally excitable peripheral nerve fibers. This results in a decrease of allodynia and hyperalgesia.[8] Lidocaine 5% patch is registered for the treatment of neuropathic pain in several countries and its numbers needed to treat (NNT) is ~4.[9] The patch needs to be replaced every 12 hours, with patch-free intervals of at least 12 hours and cannot be used on wounds, ulcers, damaged, or inflamed skin, commonly seen in patients with diabetic neuropathy. Guidelines recommend lidocaine patch in elderly as a first-line treatment, especially if there are concerns about the CNS side effects of oral medications.[10] One study shows that topical lidocaine gives no rise to cognitive impairment in elderly, whereas oral analgesics do.[11]

Capsaicin is thought to cause desensitization and denervation, the latter through reversible retraction of the nerve endings induced by TRPV1 receptor activation, leading to an overall long-term reduction of pain.[12] Capsaicin 8% patch, however, has the disadvantage that it can provoke or increase burning pain and often needs to be combined with a local anesthetic. The patch has to be applied once every 3 months in a pain clinic. Its NNT is disappointingly low, between 6 and 12.[13,14] Topical capsaicin 0.025%–0.075% cream has the disadvantage that it has to be applied 3–4 times daily during 5–6 weeks, its NNT is ~7, and considerable side effects, such as burning, stinging, or erythema, complicate its use.[15] Because capsaicin is lipophilic and usually is emulsified in a cream, thorough hand washing or the use of hand gloves is necessary to avoid irritation of eyes and/or mucous membranes, all leading to decrease in patient compliance.

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 is suboptimal. Topical creams do not have this disadvantage, thus are much easier to apply. Analgesics, such as ketamine, amitriptyline, clonidine, baclofen, and gabapentin, have been used as standalone topical formulations and in various combinations, compounded in creams, gels, or ointments.[16–18] We have been working with such compounding creams in our clinic for neuropathic pain since 2009.[19] Our experience is that it is unpredictable whether a topical analgesic in an individual patient will lead to sufficient pain reduction. To optimally select a cream leading to a higher chance of a positive response, we mostly test two creams on two selected areas of neuropathic pain, while patients sit in the waiting room. Responders will usually detect a clear pain reduction within 20–30 minutes and are able to point out which analgesic cream has superior effects.

In our endeavor to find new, more effective and safe topical creams, we discovered that the classical compound phenytoin, also known as diphenylhydantoin or 5,5-diphenyl-2,4-imidazolidinedione, administered as a topical cream of 5% or 10%, could reduce neuropathic pain in a clinically meaningful way without causing side effects. Phenytoin is known in the clinic since 80 years, and new indications are emerging on a continuous base.[20] Topical treatment of neuropathic pain might be such a new indication for this old drug. We tested this cream in a number of patients who all were refractory for other analgesic therapies with good results. The stability of the cream was also excellent, and prototypes have been stable now for 12 months.

We describe the clinical effects of this new compounded phenytoin cream in three patients, who presented themselves in our clinic for neuropathic pain, and who were treatment resistant for other analgesic treatments.

Phenytoin cream: description of three cases

Antiepileptics are effective systemic analgesics for neuropathic pain, and pregabalin and gabapentin are most well known in this class. However, in our hands, topical gabapentin 10% cream was not very effective. Therefore, we selected one of the most senior of all antiepileptics, phenytoin, which targets, among others, the voltage-gated sodium channels as the active pharmaceutical ingredient for a new compounded topical cream.[21] Topical phenytoin had an impressive analgesic effect as described in the following cases. All patients signed an informed consent for approval to publish their cases on topical phenytoin anonymously.

Case 1: diabetic neuropathic pain

A 69-year-old male suffered since 2007 from peripheral neuropathic pain in both fore feet due to diabetes mellitus type II. He scored his average pain as 9 on the 11-point

Numerical Rating Scale (NRS). His pain was characterized by burning, electric shocks, tingling, pins and needles, allodynia when soft stroking, and hand in hand, there was a numbness (anesthesia dolorosa in the pain area). Especially, his allodynia on his left foot was bothering him in the night, and he scored this annoying symptom with 10 on the NRS. Pregabalin 75 mg twice daily did not have any effect. We prescribed compounded ketamine 10% cream.[22] This resulted in a reduction of allodynia to 3 on the NRS, within 25 minutes after application. The reduction of pain lasted 6 hours, after which he woke up and had to apply the cream again. Phenytoin 5% cream reduced the allodynia and other pain symptoms to 3 on the NRS with an onset of action of 5 minutes with the duration of effect of 8 hours. After application of phenytoin 10% cream, he did not experience allodynia or other pain symptoms during the night anymore (0 on the NRS). The pain reduction appeared within 5 minutes after application and was maintained for at least 12 hours. The patient applied the phenytoin 10% cream two times daily during a period of 3 months.

Case 2: combined chronic idiopathic axonal polyneuropathy (CIAP) and pain due to chemotherapy-induced polyneuropathy (CIPN)

A 71-year-old male suffered since 2008 from CIAP, which worsened after chemotherapy vincristine for the treatment of a non-Hodgkin lymphoma in 2010. The characterization of the pain was tingling, pins and needles, electric shocks, burning and cramps within the legs, as well as anesthesia dolorosa. He scored the pain as 8 on the NRS. We tested our compounded creams: baclofen 5%, amitriptyline 5%, and clonidine 0.2%.[16,17,23,24] However, none of these creams could reduce the pain totally, though he experienced adequate analgesia (2–4 on the NRS) the following 2 years. In 2013, prostate cancer was diagnosed for which he underwent local radiation therapy, and he also received the antitestosterone agent leuprorelin (Eligard®). His neuropathic pain in his right foot recurred and the prescribed analgesic creams lost most of their analgesic effects. Phenytoin 5% cream, however, could reduce the tingling, pins and needles, and burning pain within 20 minutes, and the effect was scored as a reduction of pain from 8 to 3 on the NRS. He also perceived a cooling effect of phenytoin 5% cream, and the duration of the effect was longer than the other analgesic creams, at least 5 hours. His sleep quality improved considerably. Before the use of phenytoin 5% cream, he scored 6 on the NRS with regard to interference of his pain on his sleep (0 no interference and 10 complete interference). After application, he scored 0 on the NRS. The patient applied the cream three times daily during a period of 2 months.

Case 3: CIPN

In May 2016, a 54-year-old female received chemotherapy treatment (bortezomib) because of immunoglobulin light chain amyloidosis. Due to neuropathic pain in both hands, the treatment had to be stopped after five injections. The neuropathic pain in the hands diminished; however, the patient developed neuropathic pain in both feet in May 2016. She described her pain as burning, painful cold, tingling, and pins and needles. The patient received gabapentin 2000 mg daily, oxycodone 20 to 30 mg daily to reduce the pain, though she scored still 8 on the NRS in August 2016. Other medications, such as amitriptyline and tramadol, did not have any analgesic effect. The patient had difficulties with sleeping due to the pain. Physical examination revealed hypesthesia for pinprick and touch and allodynia. The sensation of warm and cold was disrupted in her feet up to her ankles. Her vibration sense was absent from feet up to her knees. Her ankle jerk reflexes were absent.

Test applications with analgesic creams revealed that baclofen 5% cream had a more profound pain reducing effect compared with two other compounded analgesic formulations: clonidine 0.2% cream and lidocaine 3% combined with isosorbide dinitrate 0.4% cream. The pain could be reduced to 3 on the NRS, although allodynia was still present. Following ketamine 10% cream application, allodynia disappeared.

In September 2016, the patient received phenytoin 5% cream and was asked to compare the pain reduction of this new cream with baclofen 5% cream. Before application of both creams, she scored her pain 7 on the NRS. The time of onset for baclofen 5% cream was 20 minutes and for phenytoin 5% cream was 30 minutes. The patient scored her pain reduction for baclofen 5% cream from 7 to 3 on the NRS and for phenytoin 5% cream from 7 to 0 on the NRS. The duration of the effect of phenytoin 5% cream was 4 hours. This effect resulted in a reduction of oxycodone from 20 to 10 mg daily, and gabapentin from 2000 to 1600 mg daily. She applied the phenytoin 5% cream three times daily during 1 month.

In October 2016, she received phenytoin 10% cream to test whether a higher concentration of phenytoin resulted in a more profound effect. After application of the phenytoin 10% cream, the time of onset for analgesia decreased, and within 10–15 minutes she experienced a reduction of pain from 7 to 0 on the NRS. Furthermore, duration of the effect was increased to 6 hours after the new phenytoin 10% cream

application. The patient applied the cream two times daily during 1 month.

Side effects

None of the previously described patients reported any local or systemic side effects.

Discussion

To our knowledge, this is the first report of the efficacy and safety of topical 5% and 10% phenytoin cream in reducing neuropathic pain. Oral use of phenytoin for patients with facial neuralgia was first described in 1942 by Bergouignan.[25] Low-quality small randomized controlled trials (RCTs) (n=40 and n=12) of oral phenytoin for diabetic neuropathic pain had mixed results.[26,27] An interesting double-blind crossover RCT with intravenous infusion of 15 mg/kg phenytoin over a 2-hour period showed significant reduction in neuropathic pain.[28] This reduction in overall pain persisted for 1 day after infusion, whereas 4 days after infusion, shooting pain was still reduced. Pain relief with phenytoin in this study was significantly longer than both the infusion period and the plasma half-life of phenytoin. This was a major argument for us to select phenytoin for a topical cream. Other topical analgesic creams gave overall good pain reduction, though sometimes patients had to apply the analgesic cream every other hour to maintain the analgesic effect.

The use of topical phenytoin is known for the reduction of pain due to superficial burns and chronic leg ulcers.[29] Topical phenytoin is also known to accelerate wound healing.[30,31] However, the analgesic effect of topical phenytoin in neuropathic pain has never been reported, and thus seems to be totally overlooked. The basis of the topical phenytoin formulation is a nongreasy moisturizer and does not contain any perfumes. To date, not all our patients were responders to phenytoin cream. Double-blind controlled trials are needed to reveal the NNT.

One of phenytoin's side effects, the gingival overgrowth, resulted in the focus on wound healing.[32] Wounds (in rat models) treated with topical phenytoin, tissue edema, and inflammatory cell infiltration were significantly decreased; epidermal growth factor, vascular endothelial growth factor, and transforming growth factor-β were significantly increased.[33,34]

As phenytoin is an established anticonvulsant since 80 years, most mechanistic studies have been conducted in the 60s, 70s, and 80s of last century.[20] Its mechanism of action is not yet completely understood, and most authors focus only on the inhibitory effects of phenytoin in voltage-activated sodium channels, leading to reduction of firing of depolarized neurons.[21] It is thought that phenytoin blocks sodium channels poorly at slow firing rates allowing normal activity, but suppresses the high-frequency repetitive firing.[21] Phenytoin (IC_{50}=40 μM) has six times stronger sodium channel binding activity than lidocaine (IC_{50}=240 μM).[35] Voltage-dependent L-type calcium channels are also inhibited by phenytoin.[36] Furthermore, phenytoin potentiates gamma-aminobutyric acid (GABA)-induced current through modulation of the $GABA_A$ receptor in the nanomolar range.[37]

Conclusion

Our cases demonstrate that topical applied phenytoin cream can reduce neuropathic pain considerably, sometimes even better than other topical analgesics and in this case series in nonresponders to various other analgesics. The analgesic potential of topical phenytoin cream 5%–10% in neuropathic pain should be evaluated in well-controlled randomized clinical trials.

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. Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. *Neurology*. 2007;68(15):1178–1182.
2. Lukas K, Edte A, Bertrand I. The impact of herpes zoster and postherpetic neuralgia on quality of life: patient-reported outcomes in six European countries. *Z Gesundh Wiss*. 2012;20(4):441–451.
3. Cheng JK, Ji RR. Intracellular signaling in primary sensory neurons and persistent pain. *Neurochem Res*. 2008;33(10):1970–1978.
4. Baron R, Hans G, Dickenson AH. Peripheral input and its importance for central sensitization. *Ann Neurol*. 2013;74(5):630–636.
5. Sawynok J. Topical analgesics for neuropathic pain: preclinical exploration, clinical validation, future development. *Eur J Pain*. 2014;18(4):465–481.
6. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162–173.
7. Gharibian D, Polzin JK, Rho JP. Compliance and persistence of antidepressants versus anticonvulsants in patients with neuropathic pain during the first year of therapy. *Clin J Pain*. 2013;29(5):377–381.
8. Mick G, Correa-Illanes G. Topical pain management with the 5% lidocaine medicated plaster – a review. *Curr Med Res Opin*. 2012;28(6):937–951.
9. Meier T, Wasner G, Faust M, et al. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. *Pain*. 2003;106(1–2):151–158.
10. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2010;17(9):1113–1123.
11. Pickering G, Pereira B, Clere F, et al. Cognitive function in older patients with postherpetic neuralgia. *Pain Pract*. 2014;14(1):E1–E7.

12. Uceyler N, Sommer C. High-dose capsaicin for the treatment of neuropathic pain: what we know and what we need to know. *Pain Ther*. 2014; 3(2):73–84.
13. Jay GW, Barkin RL. Neuropathic pain: etiology, pathophysiology, mechanisms, and evaluations. *Dis Mon*. 2014;60(1):6–47.
14. Derry S, Sven-Rice A, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev*. 2013;2:Cd007393.
15. Derry S, Lloyd R, Moore RA, McQuay HJ. Topical capsaicin for chronic neuropathic pain in adults. *Cochrane Database Syst Rev*. 2009; 4:CD007393.
16. Kopsky DJ, Hesselink JM. High doses of topical amitriptyline in neuropathic pain: two cases and literature review. *Pain Pract*. 2012; 12(2):148–153.
17. Kopsky DJ, Keppel Hesselink JM. Neuropathic pain as a result of acromegaly, treated with topical baclofen cream. *J Pain Symptom Manage*. 2013;46(4):e4–e5.
18. Kopsky DJ, Keppel Hesselink JM, Bhaskar A, Hariton G, Romanenko V, Casale R. Analgesic effects of topical ketamine. *Minerva Anestesiol*. 2015;81(4):440–449.
19. Kopsky DJ, Keppel Hesselink JM. A new combination cream for the treatment of severe neuropathic pain. *J Pain Symptom Manage*. 2010; 39(2):e9–e10.
20. Keppel Hesselink JM, Kopsky DJ. Phenytoin: 80 years young, from epilepsy to breast cancer, a remarkable molecule with multiple modes of action. *J Neurol*. Epub 2017 Jan 12.
21. Thorn CF, Whirl-Carrillo M, Leeder JS, Klein TE, Altman RB. PharmGKB summary: phenytoin pathway. *Pharmacogenet Genomics*. 2012;22(6):466–470.
22. Keppel Hesselink JM, Kopsky DJ. Treatment of chronic regional pain syndrome type 1 with palmitoylethanolamide and topical ketamine cream: modulation of nonneuronal cells. *J Pain Res*. 2013;6: 239–245.
23. Keppel Hesselink JM, Kopsky DJ, Sajben NL. Vulvodynia and proctodynia treated with topical baclofen 5% and palmitoylethanolamide. *Arch Gynecol Obstet*. 2014;290(2):389–393.
24. Kopsky DJ, Liebregts R, Keppel Hesselink JM. Central neuropathic pain in a patient with multiple sclerosis treated successfully with topical amitriptyline. *Case Rep Med*. 2012;2012:471835.
25. Bergouignan M. Cures heureuses de nevralgies faciales essentielles par le diphenylhydantoinate de soude. *Rev Laryngol Otol Rhinol*. 1942; 63:34–41.
26. Chadda VS, Mathur MS. Double blind study of the effects of diphenylhydantoin sodium on diabetic neuropathy. *J Assoc Physicians India*. 1978;26(5):403–406.
27. Saudek CD, Werns S, Reidenberg MM. Phenytoin in the treatment of diabetic symmetrical polyneuropathy. *Clin Pharmacol Ther*. 1977; 22(2):196–199.
28. McCleane GJ. Intravenous infusion of phenytoin relieves neuropathic pain: a randomized, double-blinded, placebo-controlled, crossover study. *Anesth Analg*. 1999;89(4):985–988.
29. Argoff CE. Topical analgesics in the management of acute and chronic pain. *Mayo Clin Proc*. 2013;88(2):195–205.
30. Shaw J, Hughes CM, Lagan KM, Bell PM. The clinical effect of topical phenytoin on wound healing: a systematic review. *Br J Dermatol*. 2007;157(5):997–1004.
31. Baharvand M, Mortazavi A, Mortazavi H, Yaseri M. Re-evaluation of the first phenytoin paste healing effects on oral biopsy ulcers. *Ann Med Health Sci Res*. 2014;4(6):858–862.
32. Arya R, Gulati S. Phenytoin-induced gingival overgrowth. *Acta Neurol Scand*. 2012;125(3):149–155.
33. Simsek G, Ciftci O, Karadag N, Karatas E, Kizilay A. Effects of topical phenytoin on nasal wound healing after mechanical trauma: an experimental study. *Laryngoscope*. 2014;124(12):E449–E454.
34. Sayar H, Gergerlioglu N, Seringec N, Ozturk P, Bulbuloglu E, Karabay G. Comparison of efficacy of topical phenytoin with hypericin in second-degree burn wound healing: an experimental study in rats. *Med Sci Monit Basic Res*. 2014;20:36–46.
35. Wang Y, Jones PJ, Batts TW, Landry V, Patel MK, Brown ML. Ligand-based design and synthesis of novel sodium channel blockers from a combined phenytoin-lidocaine pharmacophore. *Bioorg Med Chem*. 2009;17(19):7064–7072.
36. Patejdl R, Leroux AC, Noack T. Phenytoin inhibits contractions of rat gastrointestinal and portal vein smooth muscle by inhibiting calcium entry. *Neurogastroenterol Motil*. 2015;27(10):1453–1465.
37. Granger P, Biton B, Faure C, et al. Modulation of the gamma-aminobutyric acid type A receptor by the antiepileptic drugs carbamazepine and phenytoin. *Mol Pharmacol*. 1995;47(6):1189–1196.