



International Journal of Pain & Relief

Case Report

Topical Phenytoin Cream in Small Fiber Neuropathic Pain: Fast Onset of Perceptible Pain Relief - @

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Submitted: 12 October 2017; **Approved:** 04 November 2017; **Published:** 01 November 2017

Cite this article: Keppel Hesselink JM, Kopsky DJ. Topical Phenytoin Cream in Small Fiber Neuropathic Pain: Fast Onset of Perceptible Pain Relief. *Int J Pain Relief*. 2017;1(1): 015-019.

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ABSTRACT

Small Fiber Neuropathy (SFN) is a recently recognized peripheral neuropathic pain syndrome, consisting of length-dependent and length-independent varieties. Localized neuropathic pain can occur in both types: idiopathic and secondary forms of SFN exist, the latter for instance in chemotherapy induced peripheral neuropathy in diabetic neuropathy. We will describe the clinical response of 5 patients suffering from neuropathic pain linked to length-dependent small fiber neuropathy who were treated with a newly developed phenytoin cream, with the main focus on the onset of perceptible pain relief. Three patients were suffering from small fiber neuropathy and had a history of sarcoidosis. In all cases, the onset of action to noticeable pain relief was within 20 minutes and within 10 minutes in 4 out of 5 cases. The tolerability was excellent and no adverse events were reported.

Keywords: Small Fiber Neuropathy; Pain; Treatment; Phenytoin; Onset of action

INTRODUCTION

In 2015 we started documenting patients in our clinic who were suffering from peripheral neuropathic pain and were being treated with a new topical analgesic formulation consisting of 5% and 10% phenytoin cream. As early as 1937 phenytoin was introduced in the clinic as a powerful anticonvulsant, and which has been repositioned in a great number of indications since [1]. The compound emerged as a multipurpose drug due to its broad spectrum of mechanisms of action [2].

We collected detailed information of the clinical response of more than 70 neuropathic pain patients on phenytoin cream. Most of these patients were suffering from diabetic neuropathy, Chemotherapy-Induced Peripheral Neuropathy (CIPN), Chronic Idiopathic Axonal Polyneuropathy (CIAP), and Small Fiber Neuropathy (SFN).

SFN is a relatively new recognized syndrome, mostly of unknown origin, just as CIAP. However, signs of small fiber involvement can be found in many peripheral localized neuropathic pain conditions.

More than a decade ago, Katz, et al. pointed out that many physicians have observed that no matter how long patients have suffered from pain, the patient will nearly always ask "How long will it take to work?" when starting a new treatment [3]. They also pointed out that it is quite surprising that there are no accepted guidelines for studying the onset of analgesic effect, which is still the case anno 2017. In order to contribute to this important patient-centered issue, we herewith present the data of 5 patients suffering from pain in SFN that are related to the onset of perceptible pain relief after application of phenytoin cream. The numbers in brackets refer to patient numbers allocated to individual patients in our fast-growing data pool. Three patients had a history of sarcoidosis, further supportive for the diagnosis SFN [4]. In most cases the diagnosis SFN was affirmed by neurologists based on clinical history, physical examinations and neurological signs, or based on the SFN score and additional tests such as the warm water rippling test. Skin biopsies for confirmation were not taken, as such biopsies still have no therapeutic consequences.

CASE DESCRIPTIONS

Patient 1 (11)

A 57-year-old male suffered from SFN and renal insufficiency since 2014. The main pain location was in both feet and hands, and the patient scored his pain severity as 6-7 on the 11-point Numerical Rating Scale (NRS). The pain characteristics were burning pain, tingling and coldness. Previous analgesic use was pregabalin, though due to side effects the current therapy comprised of low dose pregabalin. Ketamine 10% cream reduced the pain, though aggravated tingling. We added phenytoin 10% cream to ketamine

10% cream. The amount per application was 0.8 fingertip unit (0.5 grams), and the reported onset of relief was 5 minutes. The pain after the application of cream was 3 on the NRS. The duration of analgesic effect was around 24 hours, and the patient applied the cream once daily. He has used the cream for 4 months and has not reported any adverse events.

This patient experienced an analgesic effect of the ketamine cream application, however he complained that the tingling increased. This aggravated tingling provoked by ketamine 10% cream disappeared entirely after applying the phenytoin 10% cream, and the overall results were described by the patient as: "It feels now peaceful and quiet in the area where cream was applied". Walking and standing provoked much less pain after the cream application, and patient reported a 40% improvement of pain while standing and walking.

Thus, without the patient knowing which cream was applied, the ketamine 10% cream reduced the pain but did not reduce tingling and coldness, and even seemed to enhance some tingling, while the phenytoin 10% cream decreased the tingling as well as the coldness and enhance the pain killing effect of ketamine, adding to it a very fast action of onset of around 5 minutes. The analgesic effect lasted much longer than with the ketamine 10% cream alone (ketamine alone induced analgesia for only some hours), while the addition of phenytoin significantly enhanced the duration of action, namely up to 24 hours.

Patient 2 (18)

A 62-year-old male suffered from SFN, lupus erythematoses and sarcoidosis. The main pain locations were feet, lower legs and lower arms and hands, the pain characteristics were burning and stinging. The Small Fiber Neuropathy Screening List score was 51, and the warm water rippling test was positive. There were no signs of neurosarcoidosis on the MRI. The neurologist reported a "very disabling small fiber neuropathy" in a letter of 31 January 2017.

He scored his pain as 8 to 9 on the NRS. Previous analgesic use was pregabalin 525 mg daily and oxycodone 10 mg as needed. Phenytoin 10% cream was prescribed and the patient applied a 30 gram tube of phenytoin cream over a 4 to 5 day period, thus 6.7 gram once daily. Reported onset of action was 10 minutes and scored his pain after application with a 4 to 5 on the NRS. The patient has used the cream since 6 February 2017, ongoing. No side effects were reported. In an email of 8 March 2017, the patient wrote us that:

1. Pain is reduced after approximately 5/10minutes.
2. The analgesic effect lasts about 20 hours and almost no need to apply extra during the day.
3. Sleep is 60/70% improved, before application I remained 4 out of 5 nights a week awake.

4. Stability is much better and I can now walk a bit further. Tingling is also less.

The phenytoin plasma level was below the limit of detection, analyzed after 25 days of application once daily, and the last application before plasma sampling was 2.5 hours.

Patient 3 (19)

A 74-year-old male suffered from burning pain due to SFN since end of 2014. At the age of 25 he endured a hepatitis A infection which was treated with prednisone and isonicotinyhydrazide. Further medical history was hypertension since 2006, paroxysmal atrium fibrillation in 2007, and bursitis trochanterica in 2007. Previous analgesic use was pregabalin 300 mg daily.

The main pain locations were both legs and left foot, and scored the pain with a 6 on the NRS. Within 10 minutes after the phenytoin 10% cream application of one fingertip unit containing 0.6 gram phenytoin cream, the patient experienced an onset of pain relief. After application the patient rated his pain as 1 to 2 on the NRS, and the duration of analgesic effect was around 12 hours. The patient applied cream twice daily. Since 12 February 2017 the patient uses the cream without having reported any adverse events. The phenytoin plasma level was below the limit of detection.

Patient 4 (57)

A 56-year-old female was diagnosed by neurologist with SFN in October 2015. The patient has a history of an excision of a melanoma in 1988, a Cesarean section in 1991, and colitis ulcerosa since 2006. The current medication is mesalazine 1500 mg twice daily and trazodone 50 mg before sleeping.

The main pain location was the dorsal area of both hands, and the pain characteristics were burning, painful cold, and pins and needles, without numbness. A physical examination revealed hypoesthesia for pin prick and touch in the reported area. The patient graded her pain intensity 7.5 on the NRS. Phenytoin 10% cream was applied in a dose of 0.5 fingertip unit and the onset of perceptible pain relief was 5 minutes. The pain intensity after application was reduced to 2.5 on the NRS. The duration of analgesic effect was 8 hours, and the patient applied cream twice daily. Since 7 July 2017 she has continued to use the cream. Any adverse effects were not reported.

During a telephone call on 25 August 2017 she reported that during the first weeks she applied the phenytoin 10% cream twice daily. She reported that after 3 to 4 weeks of use, the pain intensity in general was reduced further and this effect seemed long lasting, resulting in the fact that she no longer needed to apply the cream. She proceeded to use the cream only when needed. Numbness at the dorsal sides of her hands remained as a residual symptom.

In an email of 29 August 2017, she wrote: "I'm happy with the phenytoin cream; when I feel a 'nettle feeling' arising in my hands, I then apply a thin layer of cream and so far, I could prevent pain from getting intense. The cream calms awkward feelings and weakens the pain within 30 minutes. It's really a huge benefit for me."

Patient 5 (59)

A 77-year-old female suffered from SFN since 2001. She also developed hypothyroidism for which levothyroxine 100 mcg daily was prescribed, and in 2012 sarcoidosis was diagnosed. The main pain location was both feet up to 10 cm above the ankles, and the patient scored the pain a 6 on the NRS. She characterized her pain

as burning with numbness, and cramping, especially in the left foot. Physical examination revealed hypoesthesia for pin prick and touch, warmth and cold discrimination were absent up to the middle of the lower legs and vibration sensation was absent up to the knees.

Previous pregabalin use induced too many side effects, and amitriptyline 10% cream lead to worsening of burning and stabbing pain up to 7 on the NRS.

After applying the phenytoin 10% cream, the pain was reduced to 3 on the NRS and the onset of pain relief was 18 minutes. The duration of analgesic effect was 6.5 hours and the patient has applied 2-3 times daily, since the first use on 27 June 2017.

ONSET OF ACTION

In table 1 we summarized the clinical effects of applying phenytoin 10% cream on painful areas: the pain reduction was 50% or higher, clearly a clinical meaningful response. In all cases the onset to notable pain relief was within 20 minutes. The duration of action varied between 6.5 hours and 24 hours and patients applied the cream 1 to 3 times a day.

No adverse events were reported in any of the patients. In two cases, we measured the phenytoin plasma levels after few hours of application to ensure sampling around T-max: in these cases, the plasma level was below the limit of detection. In Case #1 we demonstrated that the addition of phenytoin 10% on top of an already installed ketamine 10% cream could increase the duration of action, reduce the onset of perceptual pain relief and enhance the analgesic effects.

DISCUSSION

SFN leads to burning pain, most often felt in the skin. In general, patients tell us that they like to apply the cream where it hurts. In our entire data pool to date consisting of more than 70 patients, we have monitored a relatively fast onset of perceptible pain relief after applying phenytoin cream, mostly within 30 minutes. In SFN we also monitored such fast onset of perceptible pain relief, and some patients even reported such onset within 5 minutes after application. Of course, these data are not based on randomized placebo-controlled trials and should be regarded as practice-based evidence only.

Elsewhere, we have elaborated on the mechanism of action of topically applied analgesic formulations, and have defined 3 cell types responsible for such action: small nerve fibers, keratinocytes and immune-competent cells, all part of the epidermal compartment of the skin [5]. Moreover, there are some indicators that hair follicles also play a role, perhaps as a drug reservoir, slowly releasing the active compound into the epidermis [6]. Recently, it was found that lipophilic co-analgesics such as nortriptyline and clomipramine were

Table 1: Results of the application of phenytoin 10% cream in pain in SFN in 5 patients.

Patient #	Onset of relief in minutes	Baseline NRS	After application NRS	Percentage of pain relief	Duration of effect in hours
1	5	6.5	3	54%	24
2	10	8.5	4.5	47%	24
3	10	6	1.5	75%	12
4	5	7.5	2.5	67%	8
5	18	6	3	50%	6.5

taken up quickly by these follicles, suggesting an extra-appendage pathway for skin delivery [7]. Although follicles occupy only approximately 0.1% of the skin area, this pathway has been proven to be important for the selected permeation of lipophilic compounds in the skin compartments via sebum, an oily substance of the pilosebaceous glands that spreads inside the hair follicles (Figure 1) [8]. One reason why applying phenytoin cream could lead to a fast onset of perceptible pain relief might be related to the fact that the primary targets of phenytoin, the sodium channels of nociceptors, keratinocytes, immune-competent cells, and hair follicles, are all residing in the epidermis (Figure 2). A further argument for a topical mechanism of action is the absence of detectable phenytoin in the blood.

Phenytoin is a small lipophilic molecule with a molecular weight less than 300 Dalton; this molecule seems able to penetrate quickly into

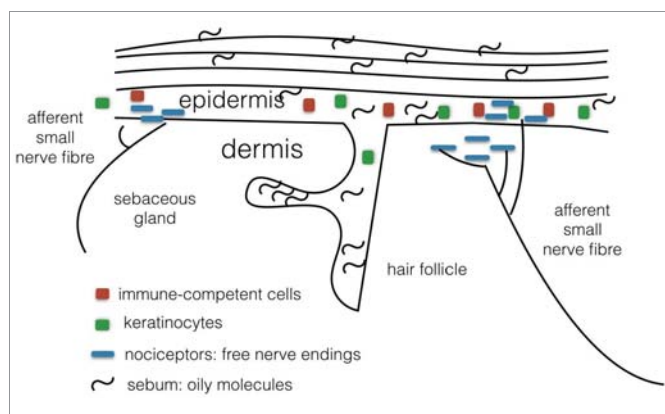


Figure 1: Fatty molecules (sebum) and hair follicles serve as reservoirs for fatty analgesics such as phenytoin to reach the epidermal target cells and downregulate peripheral wind up mechanisms. Lipophilic analgesics can accumulate in hair follicles and sebum and be slowly released from such compartments in order to reach the sodium channel containing targets in the epidermis: free nerve endings, keratinocytes and immune-competent cells.

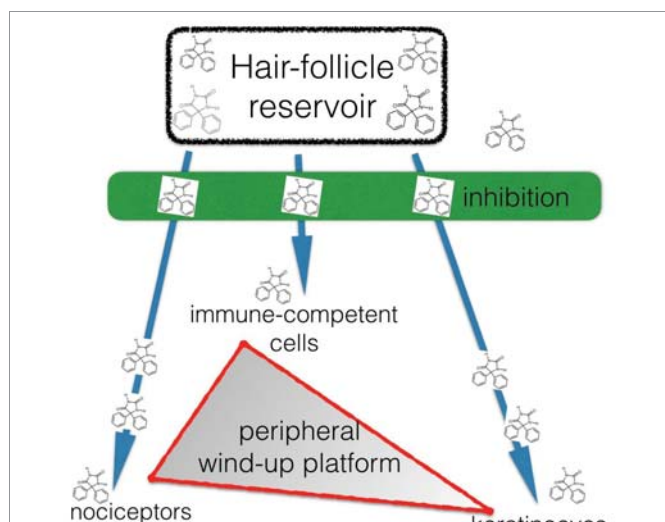


Figure 2: Phenytoin inhibits peripheral analgesic mechanisms in SFN residing in the epidermis. Targets for analgesia reside in the epidermal layers of the skin: hair follicles (reservoir function) and 3 tissues all containing sodium channels: free nerve endings (nociceptors), keratinocytes and immune-competent cells. In this figure, direct free penetrating phenytoin molecules and phenytoin released from the intra-follicular reservoirs inhibit 3 target tissues, thus reducing peripheral wind up phenomena leading to burning pain.

the various skin compartments. Phenytoin has multiple mechanism of actions, mainly acting as a broad channel blocking agent, especially for many subtypes of sodium channels [1]. Moreover, there are a number of indicators for phenytoin as a neuroprotective agent [9]. In a number of case reports we have documented the safety and efficacy in individual cases of localized neuropathic pain [10-12].

Here we specifically focused on the action of perceptible pain relief. Patients have let us know that a fast action of onset helps them confine their hopes in the further and future relief of pain. Clearly, the faster the onset of action of perceptible pain relief, the more likely will be the compliance with therapy. We prefer patient-related definition for the onset of action by asking them how long it took to perceptible pain relief, rather than arbitrary pain relief definitions such as 1-point reduction in the daily pain score relative to baseline [13].

Most co-analgesics for neuropathic pain are characterized with a slow onset of action, days up to weeks before pain relief is notable. Furthermore, when pain reduction starts slowly, step by step, central and peripheral habituation phenomena might further blur the perceived onset of action, as well as the perceived analgesia in a steady state and adding to low compliance. It seems that the relevance of a fast onset of perceptible analgesia has been underestimated in literature to date, and that topical administered phenytoin cream might be an important new armamentarium for treating neuropathic pain due to its fast onset of action and ease of application. Clearly, more data need to be gathered, including data from randomized placebo-controlled trials.

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.

REFERENCES

- Keppel Hesselink JM. Phenytoin: a step by step insight into its multiple mechanisms of action-80 years of mechanistic studies in neuropharmacology. *J Neurol*. 2017. <https://goo.gl/h94Q11>
- Keppel Hesselink JM, Kopsky DJ. Phenytoin: 80 years young, from epilepsy to breast cancer, a remarkable molecule with multiple modes of action. *J Neurol*. 2017; 264: 1617-1621. <https://goo.gl/LqxYR1>
- Katz N, Rodgers DB, Krupa D, Reicin A. Onset of pain relief with rofecoxib in chronic low back pain: results of two four-week, randomized, placebo-controlled trials. *Curr Med Res Opin*. 2004; 20: 651-8. <https://goo.gl/R78TSL>
- Keppel Hesselink JM, Kopsky DJ. Topical phenytoin cream reduces burning pain due to small fiber neuropathy in sarcoidosis. *J Anesth Pain Med*. 2017; 2: 1-3. <https://goo.gl/HU8xSH>
- Keppel Hesselink JM, Kopsky DJ, Bhaskar AK. Skin matters! The role of keratinocytes in nociception: a rational argument for the development of topical analgesics. *J Pain Res*. 2016; 10: 1-8. <https://goo.gl/VHWK7B>
- Blume-Peytavi U, Vogt A. Human hair follicle: reservoir function and selective targeting. *Br J Dermatol*. 2011; 2: 13-17. <https://goo.gl/yEDx8F>
- Liu KS, Huang TH, Aljuffali IA, Chen EL, Wang JJ, Fang JY. Exploring the structure-permeation relationship of topical tricyclic antidepressants used for skin analgesia. *Int J Pharm*. 2017; 523: 386-397. <https://goo.gl/FEvdLL>
- Schneider D, Dennerlein K, Goen T, Schaller KH, Drexler H, Korinth G. Influence of artificial sebum on the dermal absorption of chemicals in excised human skin: A proof-of-concept study. *Toxicol In Vitro*. 2016; 33: 23-28. <https://goo.gl/WuXyKA>
- Keppel Hesselink JM, Kopsky DJ. Phenytoin: neuroprotection or neurotoxicity? *Neurol Sci*. 2017; 38: 1137-1141. <https://goo.gl/Du53LY>

10. Kopsky DJ, Keppel Hesselink JM. Topical phenytoin for the treatment of neuropathic pain. *J Pain Res.* 2017; 10: 469-473. <https://goo.gl/iyRSuL>
11. Kopsky DJ, Keppel Hesselink JM. Phenytoin in topical formulations augments pain reduction of other topically applied analgesics in the treatment of trigeminal neuralgia. *J Clin Anesth.* 2017; 38: 154-155. <https://goo.gl/kmEPb2>
12. Keppel Hesselink JM, Kopsky DJ. Topical phenytoin in neuralgic pain, peripheral modulation of central sensitization: two case reports. *J Pain Relief.* 2017; 6: 284. <https://goo.gl/6qW3YB>
13. Stacey BR, Barrett JA, Whalen E, Phillips KF, Rowbotham MC. Pregabalin for postherpetic neuralgia: placebo-controlled trial of fixed and flexible dosing regimens on allodynia and time to onset of pain relief. *J Pain.* 2008; 9: 1006-1017. <https://goo.gl/iM879t>