

A single-blind n-of-1 study evaluating 4 different doses of phenytoin in a topical analgesic cream for the treatment of peripheral neuropathic pain.

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Abstract

A topical formulation containing phenytoin has been evaluated in a single-blind N-of-1 study in a patient suffering from pain due to small fiber neuropathy. In this placebo controlled study, we evaluated the safety and efficacy of 4 different concentrations of phenytoin: 5%, 10%, 15% and 20%, compounded in a neutral cream. Subsequently, an open re-test phase followed. In both phases of the study phenytoin 20% cream was preferred by the patient. The phenytoin 20% cream was superior in the duration of analgesic effect compared to the other concentrations and placebo. There were no side effects reported.

Keywords: Topical, phenytoin, small fiber neuropathy, pain, N-of-1 study.

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Introduction

Dose-finding studies are studies with the objective of determining the optimal biological dose of a drug. Mostly these studies are phase I studies. Due to the special nature of the product phenytoin cream (old molecule, and used topically in the treatment of ulcers up to 100% phenytoin) which is compounded by our pharmacist, we are able in our clinic to conduct studies for dose-finding directly in patients.

The N-of-1 trial paradigm is in general recognized as a powerful tool for rapidly gaining information, while the ultimate goal of an N-of-1 study is to determine the optimal intervention for an individual patient using objective data-driven criteria, in our case the 11-point Numerical Rating Scale (NRS) to score the intensity of pain and the pain interference on sleep (0 is no interference, 10 is complete interference, as assessed with a subscale of the Brief Pain Inventory).

Lillie et al pointed out that N-of-1 studies are a promising way to advance individualized medicine and a method for gaining insights into comparative treatment effectiveness among a wide variety of patients [1]. They also stipulated the one issue that has been of great importance in the design of clinical studies is related to the generalizability of the results. Ensuring that a study's results are applicable to all patients is not easy, given the high heterogeneity of patients in the selected populations. N-of-1 studies focus exclusively on the optimal intervention for a single patient and thus are compatible with the ultimate goal of clinical practice: the care of individual patients. In addition, N-of-1 studies can be a very efficient and much less costly instrument if added wisely to a clinical development plan of a new intervention. N-of-1 studies should be used more frequently before embarking on full-size dose-finding and phase III studies. These studies present the possibility of dissecting a study population in smaller segments, in which the patients might be more responsive to the selected intervention. The European Union also stimulates personalized medicine, which relates to the N-of-1 studies. Personalized medicine is linked to the broader concept of patient-centered care, which takes into

account that healthcare systems need to better respond to patient needs [2].

We have explored phenytoin cream in a number of peripheral neuropathic indications [3-11]. In these case reports we presented that phenytoin 10% cream was safe and seemed to be effective in neuropathic pain related to diabetes, small fiber neuropathy, chemotherapy induced peripheral neuropathy and trigeminal neuralgia. Phenytoin cream seems to have a dose-finding curve comparing the 5% and 10% concentration though no significance was reached between the two groups [11]. Up to now, we have measured phenytoin plasma levels after the application of phenytoin 10% cream in 16 patients [11]. Most patients applied the phenytoin cream for 1 to 2 weeks to reach a steady state, however after plasma sampling was performed a steady state was usually reached 1.5 to 3 hours after the last application. No phenytoin plasma levels were detected (below the limit of detection), even after the application of 6.7 grams of phenytoin 10% cream in one case. Phenytoin is one of the oldest CNS drugs repositioned in a great number of indications [12]. This is probably due to its broad mechanism of action as a channel blocker agent [13]. The compound has not only clearly analgesic properties, but also neuroprotective ones [14]. Phenytoin influences different sodium channel containing cells in the epidermis: the nociceptors, the keratinocytes and the immune-competent cells or inflammation cells (Figure 1) [15].

Design N-of-1 cross-over single-blind dose finding study

We designed an N-of-1 single-blind cross-over dose finding study to assess the safety and efficacy of 4 different concentrations of phenytoin cream (5%, 10%, 15%, 20%) versus placebo, compounded by our pharmacist. In the past, the patient informed us that the action of onset of phenytoin creams was within 30 minutes, and the duration of action was mostly between 8 and 24 hours. We therefore decided not to include a washout phase in this study, but to select periods of 3 days for each concentration and for the placebo phase.

N-of-1 study

A 77-year-old woman suffered since 2012 from SFN, diagnosed by the neurologist. She experienced burning pain only at night in both feet and scored the pain a 6 on the NRS. Numbness was present in the same area. A physical examination revealed diminished vibration sensation at the knees and absent vibration sensation at the ankles and metatarsal joints; ankle jerk reflexes were absent and knee reflexes diminished; warmth/cold discrimination was absent up to 10 cm under the knees; hypoesthesia for pinprick and touch was present, up to 20 cm under the knees. The patient stopped the use of pregabalin because of too many side effects.

She subsequently started with the application of phenytoin 10% cream before going to bed. She reported that this often resulted in a pain reduction of 50%, from 6 to 3 on the NRS within 10 minutes of application, with a duration of around 3.5 hours. She needed to re-apply phenytoin 10% cream once more during the night because of the short duration of effect.

Single-blind phase

In order to get a more consistent picture, she was entered in an N-of-1 randomized single-blind study, starting on 7 July 2017. The burning pain was at that time was only present during the night. This single-blind study compared 4 different doses of phenytoin: 5%, 10%, 15%, 20% and placebo cream. The patient was asked to score the pain on the NRS, and pain interference on sleep (0 no interference, 10 complete interference), a subscale from the Brief Pain Inventory. The patient was instructed to apply cream from the test tubes before going to bed prior to the pain starting. For 3 consecutive days she applied cream from a test tube, starting with number 1 and ending with number 5. The total duration of the study was 15 days. She received escape therapy, a tube containing 10% phenytoin cream of which she already knew the effect. The following order of phenytoin and placebo creams was tested: 10%, 15%, placebo, 5% and 20% (Figure 2).

During the first night (9 June 2017) without applying phenytoin 10% cream, she scored her pain a 5 on the NRS and pain interference on sleep. Each consecutive night she applied the cream at around 23.30. At 03.00 she always woke up from the pain and/or the need to go to the toilet. Then she observed the pain intensity and pain interference on sleep and wrote her findings down. After the application of placebo, 5%, 10% and 15% creams, the patient then needed to apply the escape phenytoin 10% cream at 03.00.

After applying phenytoin 20% cream, the patient scored her pain at 03.00 as 3.5 on the NRS, and pain interference on sleep was clearly reduced to 1.5 on the NRS (Table 1). She did not need to apply the escape phenytoin 10% cream at 03.00 after the application of phenytoin 20% cream. She noted that the duration of analgesia after applying the phenytoin 20% cream was around 7 hours.

Thus, the single-blind N-of-1 study revealed that the application of phenytoin 20% cream resulted in the longest duration of analgesia (7 hours) and had the least interference with her sleep.

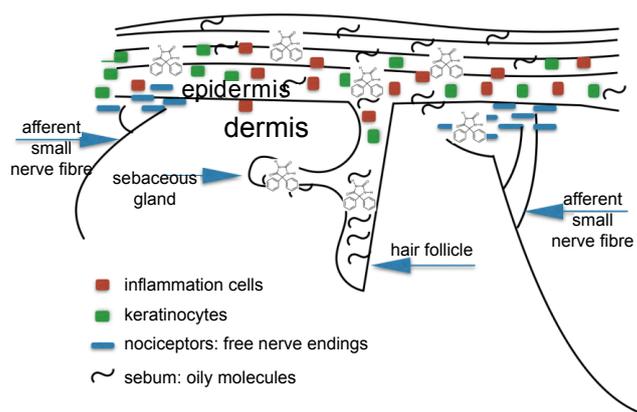


Figure 1. Phenytoin (see chemical structure formule as symbol) is a lipophilic compound, which penetrates the outer layer of the skin and will accumulate especially there where fatty molecules are present (the sebum), such as in the epidermis, the sebaceous glands and the hair follicles. From these reservoirs phenytoin can influence the various targets in the skin: nociceptors, keratinocytes and immune-competent cells..



Figure 2. Single-blind cross-over study design of 4 different concentrations of topical phenytoin (Ph) and placebo.

Table 1. Mean pain scores on the NRS.

Cream	Pain NRS (03.00)	Pain interference on sleep	Extra application at 03.00
Before application	5	5	
Placebo	5	5	yes
5%	4	4	yes
10%	5	5	yes
15%	5	5	yes
20%	3.5	1.5	no

Subsequent open re-test phase

In a subsequent new open study, the patient received tubes of 10%, 15% and 20% cream in order to observe the effect of phenytoin 10% cream on one leg and 15% or 20% cream on the other leg. The patient compared the effects of the different creams, knowing what she used. She reported on 22 September 2017 that there was no clear difference in the effect between the phenytoin 10% and 15% cream.

She then compared phenytoin 10% and 20% cream, one on each foot. She reported a clear difference in favor of phenytoin 20% cream. She chose to apply phenytoin 20% cream during the following days, and clearly did not need to use the escape cream anymore. She did not report any side effects after the application of all creams.

Discussion

Phenytoin is a nonselective voltage-gated sodium channel stabilizer. Phenytoin is orally used as an antiepileptic agent, and topically as a wound healing stimulator [16]. The neuropathic pain reducing effect of topical phenytoin as a single compound or in combination with other compounds was for the first time described in 2017 [3,4].

For the patient described above, phenytoin 20% cream was superior to the lower concentrations and placebo, without any reported side effects. For topical analgesics formulations, systemic side effects are less of a concern than for oral analgesics. Technical formulation difficulties are of greater concern when formulating higher concentrations of topical applied analgesics. N-of-1 studies can bring clarity which concentration is the best for the individual patient. N-of-1 studies are known for leading to change the prescribed analgesics and reduce costs [17,18]. Thus N-of-studies should be incorporated more often into clinical practice, and topical formulations of analgesics make such endeavors quite easy [19].

We have tested phenytoin 5% and 10% since 2015 in a population of patients suffering from peripheral neuropathic pain. Meanwhile, we have collected details on more than 8100 patients in the Netherlands.

In general, based on our experience, most patients prefer using 10% phenytoin cream as the analgesia seems to last longer [11]. In order to further explore a dose-relation we conducted the single-blind N-of-1 study described above, and in this case 20% phenytoin cream had a superior effect compared to lower concentrations and placebo. Clearly, not all patients will follow the same dose-response curve, and in our experience most patients reach satisfactory analgesia by using the 10% phenytoin cream.

In this case, the patient was given the opportunity to reevaluate the experiences gathered during the single-blind phase in a follow-up open phase. In both phases of the test the patient preferred the highest dose: 20% phenytoin cream. This dose induced analgesia for a longer period of time compared to lower dosages. This also suggests a dose-response curve, which can be regarded as proof of principle for topical phenytoin cream in localized neuropathic pain.

Phenytoin compounded in a neutral cream seems to be safe and effective in peripheral neuropathic pain. Currently we are preparing a full powered randomized placebo-controlled trial to further evaluate the safety and efficacy of phenytoin cream.

Conflict of Interest

Authors are patent holders of two patents related to the topical formulations of phenytoin in the treatment of pain:

- Topical phenytoin for the use in the treatment of peripheral neuropathic pain,
- Topical pharmaceutical composition containing phenytoin and a (co-)analgesic for the treatment of chronic pain.

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