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Case Report

The Individualized N-of-1 Trial: Dose-Response in a Single-Blind Cross-Over Response Test of Phenytoin 10% and 30% Cream in Neuropathic Pain

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Abstract

We introduce a new individualized testing paradigm to quickly identify responders for the topical treatment of peripheral neuropathic pain, based on an N-of-1 trial: a dose-response in a single-blind cross-over response test. We present a case of a patient suffering for 10 years from peripheral neuropathic pain due to diabetes mellitus type I. Two different concentrations of phenytoin cream (10% and 30%) were tested in a single-blind cross-over response test. While the placebo and phenytoin 10% creams did not result in a meaningful decrease of the pain of at least 2 points on the 11-point numerical rating scale (NRS), the single-blind application of phenytoin 30% cream reduced pain from 6.5 to 1.5 on the NRS within 5 minutes after application. The analgesic effect continued for 8 hours. This obvious pharmacological dose-response is a clear pointer for an analgesic effect of high dose phenytoin cream in this patient. No side-effects were reported.

Keywords: *N-of-1 Trial; Phenytoin; Neuropathic Pain*

Introduction

Entering the era of personalized medicine obliges new research strategies. It is increasingly clear that new clinical test paradigms are also badly needed. The time and resources consuming randomized clinical trials can only answer general questions, and many individualized problems are not solved by trials and guidelines based on such trials. Topical compounded analgesics are examples of individualized pharmacotherapy and each patient requires a tailored approach. We herewith present a new testing paradigm, following the model of an N-of-1 trial designed as a single-blind cross-over response test, which leads to such tailored approach. In this test 2 different concentrations (low and high) an active pharmaceutical ingredient (API) are tested versus placebo in one patient. Peripheral neuropathic pain is especially suitable for this test, usually due to its symmetrical distribution (e.g. both feet) and relative easiness to distinguish the difference in possible pain reduction on the 11-point numerical rating scale (NRS) between two areas. The response of a patient to the topical application of an API is usually fast, between 5 and 30 minutes.

A recent Cochrane review focused on topical analgesics for pain [1]. The definition for topical analgesics used by the Cochrane review is: "A topical analgesic medication is one applied to body surfaces such as the skin or mucous membranes to treat painful ailments; they are either rubbed onto the skin or made into patches or plasters that are stuck onto the skin".

Topical amitriptyline for instance has been used since 1981 [2] and many lines of evidence converge into a relative convincing argumentation that topically applied amitriptyline has value in the treatment of localized neuropathic pain [2]. Later studies were published supporting such topical use and assessing the transdermal delivery aspects of a number of creams [3]. A first clinical case of amitriptyline

gel described in a patient suffering from chronic pain leading to adequate plasma levels was published in 1999 [4]. Since this century, physicians have increasingly been prescribing compounded creams containing a number of analgesics, such as amitriptyline, ketamine, baclofen, clonidine [5]. In our Institute for Neuropathic Pain we have started to compound special analgesic creams since 2010, together with a compounding pharmacist [6,7]. We collected patient data via a patient-monitor – secured online survey – and this helped us to analyze the response of patients on various creams and concentrations. We have reported some of these results in previous articles. From our results, we soon deducted that creams containing APIs in a higher dose-range than usually described led to superior clinical responses. For instance, amitriptyline 10% cream was clearly superior over low dose amitriptyline formulations (1% to 5%) [8]. However, we were still not quite satisfied as some patients remain only non- or partial responders to therapy with compounded creams. We looked for a potentially better compound and discovered that the old broad acting sodium channel blocking agent phenytoin could be compounded in one of our base creams without any pharmaceutical issues. Moreover, both the phenytoin 5% and 10% creams led to favorable clinical responses [9-14]. Those patients in particular suffering from localized burning pain, such as diabetic neuropathic pain, post-herpetic neuralgia and small fiber neuropathic pain were good responders. Our detailed data pool concerning phenytoin cream currently consists of 80 patients, and besides the indications mentioned above, we saw patients suffering from a variety of other peripheral neuropathic pain states who responded favorably to the cream.

Since 2014 we have developed a number of compounded creams containing phenytoin as a stand-alone API, as well as creams containing phenytoin together with other (co-)analgesics [15].

In the history of the development of topical analgesics, starting in the 1990s, relatively low concentrations were selected and APIs were compounded mostly in pluronic lecithin organogel in order to enhance the transdermal migration of the API. For instance, in early clinical trials amitriptyline and ketamine were dosed even below 1%. We feel that one of the reasons for negative studies in the past is related to the choice of either the wrong formulation or the selection of a suboptimal dose [16]. After developing 5% and 10% phenytoin creams, we explored higher dose-ranges for efficacy and safety and pharmaceutical properties. Meanwhile, we can compound phenytoin 15%, 20%, 25% and 30% creams. The phenytoin 30% cream, as a high strength cream, has some minor drawbacks related to its smearability; patients need to receive a specific instruction as to how to apply the cream as it is a little more rigid, probably due to the high concentration of phenytoin.

We present here the first results of a single-blind response test in a patient suffering from diabetic neuropathy, with a baseline score of 7 on the NRS, who responded only partially to previously prescribed creams (amitriptyline 10%, ketamine 10%, gabapentin 10% cream). The DN-4 score (neuropathic pain screenings tool) was 8.

N-of-1 trial: single-blind cross-over dose-range response test

Single patient trials are regarded as one of the new hallmarks for individualized medicine [17]. This line of thinking and the fast onset of action of topical analgesics (within 30 minutes) helped us to develop in our clinic a new instrument to assess the response on a certain analgesic cream.

Patients who are selected to enter this single-blind cross-over dose-range response test need to suffer from peripheral localized neuropathic pain in 2 areas (e.g. both feet) with a pain intensity of at least 3 on the NRS. The baseline NRS of both areas need to be comparable and should not be more than 1 point difference in baseline NRS. When competing the required conditions, patients then receive an equal amount (e.g. a fingertip unit: 0.5 gram) of placebo cream and phenytoin 10% cream to apply on the two areas. Within 10 to 30 minutes most patients can notice the difference. If there is 2 points or more difference in pain reduction in favor of active treatment, we define the patient as a responder. The patient then receives a prescription for phenytoin 10% cream. In case of a non-responder to the active treatment, we cross-over the therapy and apply high dose (20% to 30%) to the foot previously tested with placebo cream. If patients are responders to high dose only, mostly within 5 minutes, a clear pain reduction is noticeable. Most patients who test once with this response

test remain responders on the cream for many months. One of our first patients is still using the cream after almost 3 years with stable results.

This N-of-1 single-blind cross-over response test defines the subsequent treatment phase in responders, in this case treatment with high dose phenytoin cream.

Case Presentation

A 58-year-old female suffered from DM type 1, treated with insulin, levothyroxine, glimepiride, metformin, enalapril, rosuvastatin, and as analgesics both paroxetine 60 mg and gabapentin 1200 mg daily. She had responded relatively well on various topical creams, such as amitriptyline 10%, ketamine 10%, and gabapentin 10% cream, though after some years the analgesic response was reduced. At the time she re-entered our clinic, she was treated with ketamine 10% cream because she suffered quite badly from allodynia and ketamine 10% cream seemed to be able to reduce this symptom. However, the pain slowly crept back to a baseline score of 7 to 8 on the NRS and she asked whether a new analgesic cream could help her.

Our patient received an equal amount (i.e. 0.5 gram) of placebo cream and phenytoin 10% cream to apply on the right and left foot respectively.

The given instruction before applying the creams was: "I would like to offer you to test 2 creams on the pain areas, which I believe can help to lessen your suffering without knowing how one cream exactly works. The working mechanism of the other cream is clearer, though side effects can occur. After maximally 30 minutes, you will tell us whether there is a difference in pain scoring on the NRS, and based on your evaluation we know what best to prescribe you".

After the application of both creams, the patient stated within 10 minutes there was only a 1.5 difference on the area where the placebo-cream was applied, without her being able to exactly describe this difference. The foot felt warmer and therefore somewhat less painful. The patient did not have any pain reduction in the area on which the phenytoin 10% cream was applied, therefore she was not a responder. Subsequently, we crossed-over to the application of phenytoin 30% cream on the 'placebo' foot, and within 5 minutes the patient reported an initial decrease of pain from 6.5 to 3.5 on the NRS, eventually leading to a decrease 1 to 1.5 on the NRS (see Figure 1).

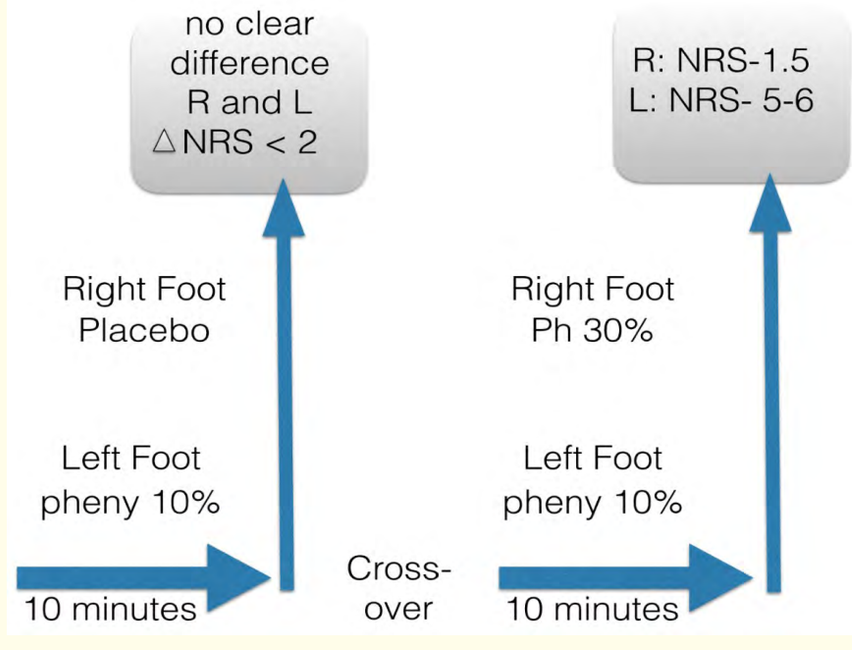

Figure 1: *A new N-of-1 single-blind cross-over response test to evaluate whether patients are responders to low dose or high dose phenytoin cream (pheny = phenytoin).*

Discussion

The development of a new testing paradigm for evaluating low and high dose compounded analgesic creams versus placebo is an example of an N-of-1 study. The cross-over design we presented enables us to differentiate between non-responders, responders to low dose phenytoin cream and responders to high dose phenytoin cream. In the past, the development of topical analgesics was severely hampered due to the absence of such dose-finding tests. For instance, the development of compounded amitriptyline-ketamine cream led to a very protracted clinical development timeline, starting in 2001 by the filing of the Epicept patent, with a phase III trial in 2007 treating chemotherapy induced peripheral neuropathic pain with a negative result. The use of a fast single-blind cross-over response test, comparing 2 different doses with placebo, can change the landscape of the development of topical analgesics. The fact that patients respond to a higher dose, and not to a lower dose or placebo in a single-blind test-design, is a further pointer for the efficacy of phenytoin cream. A high dose did not result in any side effects.

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.

Conflicts of Interest

The authors report no other conflicts of interest in this work.

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