



Rationale for the Repositioning of Phenytoin as a Topical Analgesic for Peripheral Neuropathic Pain and a Personalized and Investigator-Driven Development Plan

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Abstract

Drug repositioning is recognized as a dynamic field of drug development that can offer real benefits to patients, and it refers to the process of finding new uses for existing drugs outside the scope of the originally authorized medical indication. One key obstacle for the registration of repositioned drugs is the fact that old drugs are off-patent and therefore pharmaceutical industries will not invest in the development of new indications for these drugs because there is no financial incentive for such development. The development of an old drug for a new indication therefore needs to be performed by non-commercial parties, such as medical doctors (ideally as part of a network of experts) or academic groups. Based on external regulatory advice and after consultation with competent authorities, they then become the architects of a development plan. This paper will outline some fundamentals for such investigator-driven development for a new compounded formulation containing phenytoin in the indication peripheral neuropathic pain, and suggests a solution for funding of such a development.

Keywords: Topical; Repurposing; Personalized medicine; Neuropathy; Analgesia

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Introduction

Drug repositioning or repurposing is increasingly recognized as a dynamic field of drug development that can offer additional benefits to patients. Drug repositioning refers to the process of finding new uses for existing drugs outside the scope of the originally authorized medical indication. One key obstacle for the registration of drugs outside their authorized indication is the fact that old drugs are off-patent and therefore pharmaceutical industries in general will not invest in developments of new indications for old drugs, as there is no financial incentive for such development. The development of an old drug in a new indication therefore needs to be taken into the hands of non-commercial investigators, who, based on external regulatory advice and after consultation with competent authorities, can become the architects of such a development plan. The feasibility of executing this plan would be greatly increased if such repurposing drug project would be eligible for national grants. A national grant would become possible after drafting a development plan based on an official consultation with competent authorities. This paper will outline some fundamentals for such an investigator-driven development. Our repositioning efforts began when we found that phenytoin was a drug repositioned in a number of indications, including neuralgic pains [1-3]. This is most probably related to its main mechanism of action as a broad non-selective sodium channel blocker [4]. Drug repositioning is currently attracting a lot of attention and can become an important tool for expanding our therapeutic armamentarium at relatively low cost. The case of phenytoin demonstrates the value of an old drug for a new indication. Especially drugs characterized by 'dirty pharmacology', i.e. based on a broad receptor profile, hold promise for the treatment of many other indications than those for which they were originally approved. Peripheral neuropathic pain is a new putative indication for topical phenytoin. We developed a special compounded phenytoin cream in a concentration range of 5% to 20% in order to decrease systemic adverse events and increase the concentration of phenytoin in the epidermis where the nerve endings of the nociceptors reside. The physicians at our Institute for Neuropathic Pain (INP) and several other pain physicians and neurologists in the Netherlands have prescribed this compounded phenytoin cream since 2016 to a substantial number of patients, with good results

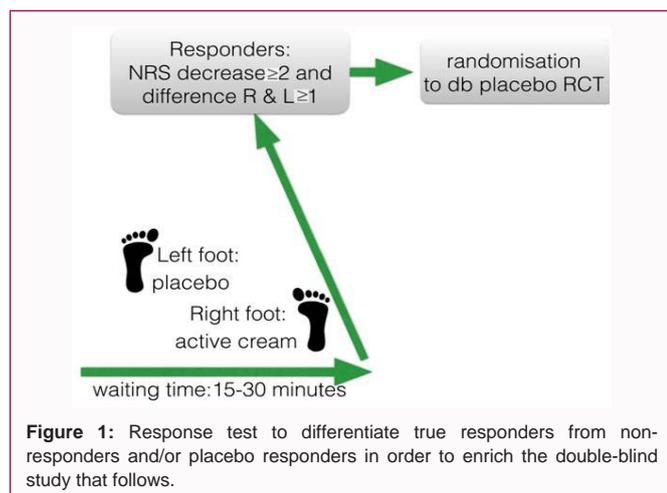


Figure 1: Response test to differentiate true responders from non-responders and/or placebo responders in order to enrich the double-blind study that follows.

and without troublesome side effects. Phenytoin cream is therefore a good example of the repositioning of an old compound in a new formulation (a cream) for a new indication: peripheral neuropathic pain. We hope to change the current off-label use of this analgesic cream in the future to approve use, based on an investigator-driven clinical development and designed after consultation with regulatory authorities. The development steps to be taken will be focused on personalized medicine, and based on individual response tests to quickly differentiate between responders and non-responders. We will discuss some data supporting this phenytoin rediscovery and personalized registration project in this paper. Investigator-driven drug development is rare, and especially in the field of drug repositioning and repurposing such development can be of great value to reduce off-label use and to rationalize new indications and/or formulations. This paper is the first paper to date to discuss the aspects of investigator-driven drug development using the modern tool of personalized medicine.

Phenytoin

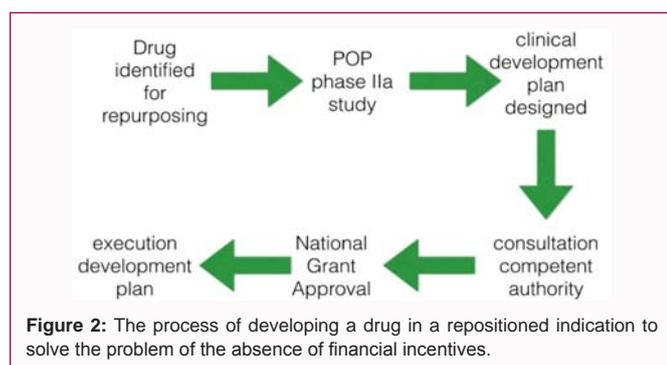
Phenytoin is one of the oldest active pharmaceutical ingredients acting as a broad sodium channel blocker and is regarded as a one of the first anticonvulsants discovered [1]. Phenytoin is still used as a golden standard drug during the quest for new and better anticonvulsants [5]. Anticonvulsant drugs are also used to treat a wide range of non-epileptic conditions, including chronic pain. Phenytoin has also become recognized as a treatment option for neuropathic pain treatment and for lead optimization in animal models for pain [6]. Phenytoin has unique pharmacological properties and has been repositioned in a great number of indications, from wound healing to bipolar disorders [7]. Phenytoin has a broad mechanism of action, one of which is the blocking of sodium channels. These channels are thought to be of key importance in the pathogenesis of neuropathic pain. Phenytoin, just as pregabalin, gabapentin, and other co-analgesics in the field of neuropathic and neuralgic pain such as carbamazepine, therefore qualifies to be explored as a therapeutic principle in neuropathic pain. In trigeminal neuralgia, we recently pointed out that phenytoin was as effective as the gold standard carbamazepine [3]. In one early (1978) double-blind, randomized, placebo-controlled trial (RCT) in Painful Diabetic Neuropathy (PDN), phenytoin 100 mg administered 3 times daily was significantly more effective in reducing pain compared to a placebo [8]. In a more recent RCT (1992) oral phenytoin 100 mg twice daily, when used alone or in combination with buprenorphine, had mild to moderate

pain relief in cancer pain patients [9]. Cancer pain is known to have a neuropathic component [10]. Furthermore, phenytoin has neuro protective properties [11,12]. In a number of peripheral neuropathic pain disorders, the pathogenesis of pain is (partly) located in the skin where nociceptors and other relevant structures reside. Most of these structures (Keratinocytes, Immune-competent cells) are thought to contribute to pain and are characterized by a great number of sodium channels [13]. The application of topical phenytoin to treat localized neuropathic pain therefore seems to be quite relevant for patients, especially since current orally administered analgesics have a low number needed to Harm (e.g. due to tolerability and adverse event issues), and most patients therefore remain insufficiently treated. Based on our work, compounding pharmacists began to develop and offer topical phenytoin formulations. These pharmacists often based their formulations on our work and refer to our articles in this field. However, there is no consistency in the formulation used (such as the base cream selected), and thus a number of different formulations are currently entering the off-label market. From our patients we received such compounded formulations. It is important to note that several of these formulations did not result in a reduction of pain. This is an extra argument for a data-driven, registration-orientated development of a selected optimal formulation of one base cream containing phenytoin to achieve a registration for such a formulation. Various other topical formulations containing phenytoin are specifically compounded to treat diabetic wounds and ulcers, such as misoprostol 0.0024% phenytoin 5% diabetic ulcer cream [14]. These creams also are not yet registered due to the absence of financial incentives, and thus variability exists in formulations used and effectiveness if pharmacists compound such creams in a non-standardized manner.

Rationale for Topical Development of Phenytoin Cream

In a number of peripheral neuropathic pain disorders, the pathogenesis of pain is (partly) located in the skin where nociceptors and other relevant structures reside, and most of these structures (keratinocytes, immune-competent cells) are thought to contribute to pain, and are characterized by a great number of sodium channels [13]. The application of topical phenytoin to treat localized neuropathic pain therefore seems to be quite relevant for patients.

Together with a compounding pharmacist, we have developed formulations of phenytoin 5% to 20% in a special topical cream. These formulations have been prescribed to patients since 2016 [15]. The compilation of a safety data pool is ongoing, to date containing data of around 100 patients, which is also important from the perspective of registration. As the safety profile for phenytoin after oral use is well known, and the compounded cream does not result in phenytoin detectable blood levels (data on file), we will argue in our discussions with the competent authorities that an extensive safety data pool for the topical formulations should not be required. Meanwhile, compounding pharmacists abroad are offering creams based on our work (similar but not identical, leading to issues as described above). In order to improve the complex off-label use-compounding situation, we believe that an official approval of a well-described formulation of topical phenytoin for the use in peripheral neuropathic pain will help to further disseminate this treatment for patients in the Netherlands and other European countries. Such an approval would help to improve the quality by defining a GMP standardized formulation, supported by adequate clinical data. Currently, we are seeking advice from the regulatory authorities for an investigator-



driven clinical development in Painful Diabetic Neuropathy (PDN). Various sodium channels are linked to the pathogenesis of PDN such as NaV1.7, NaV1.8 [16,17]. Highly selective sodium channel blockers however have recently failed in the development as analgesics in PDN. For instance, TV-45070, developed as a topical sodium channel inhibitor for the treatment of pain, failed in phase II b clinical studies [18]. Furthermore, there is no consensus which subtypes of sodium channels are most important in PDN. Thus the INP selected phenytoin, a compound with broad sodium channel blocking properties, for the formulation of a topical cream for the treatment of PDN. Phenytoin applied systemically or topically in an animal model onto neurons suppresses the generation of discharge without blocking impulse conduction [19]. These data led the investigators to conclude that the clinical analgesic action of phenytoin in these conditions may involve a direct suppression of ectopic impulses generated in the region of the nerve damage. In diabetes mellitus nerves are damaged in the region of the skin [20,21]. The first study (1968) evaluating oral phenytoin in PDN showed that from 60 patients treated, an excellent symptomatic relief of pain and paresthesia was present in 41 patients, and a fair response in 11 patients [22]. Improvement was noted from 24 hours to 96 hours after the first dose. As a feature of control when the drug was discontinued, symptoms frequently recurred. In a double-blind crossover RCT of 16 patients with PDN, 13 patients had a significant relief of pain and/or paresthesia with phenytoin 100 mg 3 times daily [23]. Therefore, based on these data, we believe that there is a firm base for developing phenytoin as a topical analgesic formulation for the treatment of peripheral neuropathic pain.

Phenytoin is Safe if applied on the Skin

In a number of animal models various phenytoin concentrations in topical vehicles were safe to apply on skin and in wounds and led to improved healing [24,25]. In models of diabetic wounds such positive therapeutic effects have also been documented, and topical phenytoin improved the healing of diabetic wounds without any signs of dermatotoxicity [26]. For 60 years phenytoin has also been applied to the wounds and skin of patients in various wound healing formulations, in concentrations up to 100%. Thus, there is a long tradition of observations and clinical studies in wound healing effectively and safely treated by phenytoin. All observations and results of the animal and clinical studies point in the same direction. Phenytoin applied topically in a range of concentrations up to 100% promotes wound healing and reduces pain without local side effects [7].

A Personalized Investigator-Driven Development Plan

We are currently designing, in close collaboration with two

academic centres in the Netherlands, a number of placebo-controlled clinical studies in peripheral neuropathic pain conditions. The enrichment strategy designed for these studies is intended to optimally personalize therapy. This design is supported by the following argumentation.

The EMA, in their News item of 07-03-2017 'Personalized medicines - focus on patients and healthcare professionals', stresses the importance of personalized medicine: "Personalized medicine is often seen as the next frontier in patient-centred health care. There is no common definition of the term, but it is often referred to as a medical model for tailoring the right therapeutic strategy for the right person at the right time, on the basis of an individual's characteristics and genetic makeup". Clearly, classical RCTs are not optimized for such personalized medicine. Personalized medicine is sometimes referred to by the EMA as 'stratified medicine'. The aims of such medicine are defined as "decreasing the number of adverse drug reactions and increasing the efficacy of drug therapy". The utility of personalized medicine is defined by the EMA as: "identify patients who are most likely to benefit" and this implies "patient selection". The analgesic cream developed by us makes a new development strategy possible based on such personalized and stratified medicine, supporting the identification of patients most likely to benefit and excluding patients who are identified as non-responders. This design is based on the fact that patients consistently report to noticing pain reduction after the application of phenytoin cream within a very short period of time (1 minute to 30 minutes). This fast response test can be seen in the analogy of the genomic biomarkers discussed in EMA papers such as 'Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle' (EMA/CHMP/800914/2016). In this paper the use of predictive biomarkers to decide treatment are recommended. The new guideline will help to optimise the co-development of medicinal products and companion diagnostics. The anticipated effect is to better define the patients in whom the benefit/risk will be positive. In the project of topical phenytoin as an analgesic, such biomarker development is bypassed by the fast response test. This test can identify whether a patient is a responder or non-responder, and it is possible to have test results within 30 minutes. It is based on the fact that in PDN patients suffer from moderate to severe pain at both feet. A single-blind or double-blind test phase, where a patient applies cream A (e.g. placebo) to one foot and cream B (e.g. verum) to the other foot, is easy to apply and only patients where the pathogenesis of the disorder is coherent with the mechanism of action of phenytoin will respond. This test-phase will decrease the heterogeneity of the population entering the double-blind phase of the study. The response is defined as a minimal pain reduction of 2 points on the 11-point Numeric Rating Scale (NRS) compared to base line in the area where the verum cream was applied, and minimally 1 point on the NRS difference between the placebo and verum cream (Figure 1). Such a test phase and the subsequent randomization phase of responders in the main double-blind phase have resemblances to the modern adaptive designs, though in our case it is applied on an individualized case-by-case basis. Such a response phase is highly relevant. A number of well-designed recent studies in PDN, evaluating New Chemical Entities (NCEs) as well as established drugs for the treatment of neuropathic pain, such as pregabalin, gabapentin and duloxetine, were negative due to amongst others an unexpectedly large placebo response [27-29]. In the GSK study of Rauck et al. [28] the placebo group had a mean pain relief of more than a 2 point reduction on the NRS at the end of

the maintenance phase (week 13). Even combinations of registered analgesics in PDN are sometimes not effective. A large, multinational combination treatment trial investigating duloxetine in combination with pregabalin in PDN, based on the fact that such a combination therapy might be a rational clinical option, failed to meet its primary objective [30]. It was pointed out that one major reason accounting for these inconclusive outcomes may be related to the fact that the heterogeneity of neuropathic pain symptoms was not sufficiently considered [30]. The heterogeneity of the PDN population in a topical treatment paradigm based on clonidine was already pointed out in 1995, which led to an enrichment design [31]. In a more recent study assessing the efficacy of topically administered clonidine, the study was negative overall. However, in the cohort of patients having an intact peripheral nociceptors function, as measured by determining the painfulness of 0.1% topical capsaicin applied to the pretibial area of each subject for 30 minutes during screening, they responded significantly better compared to the placebo [32]. In our case we do not need such painful capsaicin-related responder phase, as we have developed a more logical response test based on phenytoin cream itself. These studies point out the relevance of enriching the population to identify responders prior to randomization. This heterogeneity within this indication, as well as the high placebo-response in general, is a reason for us to exclude placebo-responders in the pre-study response test phase and only include responders. The current development plan is foreseen to include 3 studies:

Study 1

A 12-week double-blind placebo-controlled RCT with 3 treatment arms (phenytoin 10%, phenytoin 20% and placebo cream) in patients with a primary diagnosis of PDN for at least 6 months and at least moderate to severe pain (NRS \geq 4) in a total of 480 patients will be planned.

The study will follow an enrichment design, and starts with a double-blind response test in which phenytoin 10% and placebo cream will be tested in a randomized manner. Patients being a responder to phenytoin cream 10% will subsequently enter the 12-week RCT.

Study 2

An N-of-1 randomized trial series will be performed according to a comparable enrichment design, including two treatment rounds with phenytoin 10%, phenytoin 20% and placebo cream. Each treatment period lasts 2 weeks, thus the whole N-of-1 trial lasts 12 weeks. Enrichment is based on a positive response test with phenytoin 10% cream and placebo cream. After the N-of-1 trial the patient will be prescribed the active cream, when reaching significance between placebo and an active cream.

Study 3

A 6-week enrichment randomized double-blind placebo-controlled crossover trial with 3 treatment phases of 2 weeks each (phenytoin 10%, phenytoin 20% and placebo cream) in painful Chronic Idiopathic Axonal Polyneuropathy (CIAP) will be performed. The study will include 40 patients, responding to the single-blind response test.

Open extensions for treatment up to 12 months will be offered to responders in all 3 studies.

In addition, we are building up of a safety data pool consisting of patients whose data are entered on an ongoing basis.

Discussion

Drug repositioning refers to the process of finding new uses for existing drugs outside the scope of the originally authorized medical indication. One key obstacle for the registration of repositioned drugs is the fact that old drugs are off-patent and financial incentives for such developments are therefore absent. The development of an old drug for a new indication will therefore be taken into the hands of non-commercial investigators. Based on external regulatory advice and after consultation with competent authorities, the investigators will coordinate the operationalization of the development plan. As an example of such drug repositioning-development effort, we presented a draft development plan for phenytoin for the treatment of peripheral neuropathic pain. We intend to discuss this plan with the Dutch competent authority (MEB, Medicines Evaluation Board). When discussions with competent authorities lead to a positive outcome in the sense of agreement on a reasonable path towards potential approval, grants for a development plan should be provided by national grant organizations (e.g. in the Netherlands ZonMw). The investigators subsequently not only coordinate the further execution of the development plan, but with the use of a network of relevant specialists (e.g. in regulatory affairs) also prepare the dossier and function as Marketing Authorization Holders (MAH). In such a case, it would also be needed to agree pragmatic solutions for the other duties of the MAH, such as in the field of pharmacovigilance, product release and change control. Also, annual fees should be waived by the authorities and a low-cost solution for the submission of post-approval changes should be developed. A mix of models now in place for generic drugs and those to stimulate development of orphan drugs could be a starting point for a regulatory framework to facilitate repositioning of old drugs in new indications. This paper has outlined some fundamentals for an investigator-driven development for a new compounded formulation containing phenytoin in the indication peripheral neuropathic pain and might serve to further contribute to discussions in the field of the repositioning of old drugs in new indications.

Conflict of Interest

Two authors (JMKH, DJK) 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 to treat pain.

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