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Case Report

Phenytoin Cream in Painful Diabetic Neuropathy: Support for Development of New Indications for Generic Drugs Needed

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Abstract

Drug repositioning or repurposing is the use of old drugs in new indications. It is increasingly recognized as a way to identify new and cheap therapies. However, in general there is no financial incentive for the development and registration of old drugs in new indications. That is why there are currently governmental sponsored programs installed to support drug repositioning efforts initiated by investigators. Such program in the Netherlands for instance is the testing of tranexamic acid in subdural hematoma, in order to prevent operations. We started an investigator driven development of a compounded cream containing phenytoin for the topical application in painful neuropathy and completed proof of principle based on single-blind phase II a data at the end of 2017. We are currently starting phase II b studies and are outlining a development strategy in order to be able to start consulting with an EU competent authority for the purpose of obtaining registration. Compounded phenytoin cream currently can be prescribed off-label; the aim of our developmental work is to make a standardized GMP produced specialty available. We present a case of a patient suffering from painful diabetic neuropathy and discuss the rationale behind this development.

Introduction

Recently in the JAMA, it was pointed out that new indications are rarely sought for cheap generic drugs, for which it is more difficult to profit from the research [1]. Policies supporting the development of new indications for generic drugs are needed. The authors suggest that public agencies should start to prioritize funding studies of new uses of old drugs, for which pharmaceutical industry has little incentive to conduct. Various 'New Therapeutic Uses' programs are currently designed. In the Netherlands for instance, a governmental sponsored program started in 2012. The program is based on various pillars, such as Drug Rediscovery, and Personalized Medicine. Within the context of this Dutch Zon Mw program (collaboration of Care Research Netherlands) for drug rediscovery, research into the effectiveness of promising applications of existing drugs in new indications, with the ultimate goal of registering the new application, is stimulated. One such project sponsored since end of 2017 is related to the treatment of the chronic subdural hematoma with the old drug tranexamic acid. By using this drug in a pilot study in 38 patients, surgery was prevented in all treated patients. The current supported study investigates the effect of this treatment compared with placebo. Of course, one such study will not directly lead to the registration of tranexamic acid in subdural hematoma. For this consultation with an EU competent authority is needed and a registration file needs to be prepared. Consultations with EU competent authorities for investigator-driven developments are made possible, for only relatively small costs.

We started an investigator driven development of phenytoin, repositioned as a new topical formulation in Painful Diabetic Neuropathy and finished proof of principle early 2018, based on the completion of proof of principle based on phase II a studies. Here we will present one diabetic patient suffering from painful neuropathy as an example of the clinical utility of the topical phenytoin formulation.

Case Presentation

Quick analgesic response after application of phenytoin 10% cream. We present a male patient, age: 67, diagnosis of painful polyneuropathy since 2009, due to diabetes mellitus type 2, since 2005.Medical history: twice a cardiac catheterization (2006; 2017), atrium fibrillation (2014) and cardio version. Previous analgesic use: pregabalin and amitriptyline 10% cream both stopped due to absence of pain reducing effect.

The main pain location: both feet up to 15 cm above the ankle, and the pain characteristics were: burning, tingling, pins and needles. Mean base line pain score on the 11-point Numeric Rating Scale was 7.5. We tested the response of the patient by applying single-blind on one foot compounded baclofen 5% cream, and on the other foot phenytoin 10% cream. There was no analgesic response after the application of baclofen cream and a clear and fast pain reduction following the application of phenytoin cream. We thereafter prescribed a compounded cream containing 10% phenytoin. The patients applied the cream in amounts of 2 fingertip units, equal to 1.2-gram cream. The onset of action, as reported by the patient was 5 minutes. After cream application, the pain quickly was reduced to a pain NRS score of 0; only numbness remained.

Patient applied the cream 1 to 2 times a day, and started using the cream in February 2017. There was no tolerance for the analgesic

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effect, and the efficacy of the cream remained ongoing for many months since the first application. No adverse events were reported.

Discussion

The development and marketing of a new Active Pharmaceutical Principle (API) costs between 500 million and 2 billion. In addition, the average time to approval of a new drug by the registration authorities is 15 years, leaving only 5 years for patent-protected earning back the investment money and generating sufficient profits. Clearly this dictates a high price strategy for newly approved medicines. Old drugs however, due to generic erosion, are cheap and based on a long history of use, its efficacy and safety profiles are quite transparent. Phenytoin is such an old drug, already in use in the clinic for 80 years [2]. We started repositioning this drug as a topical formulation in 2015 and meanwhile treated more than 100 patients, without seeing any troublesome adverse event. The quick onset of action, within 30 minutes, supported an intradermally situated mechanism [3-5]. Plasma levels of phenytoin remained under the limit of detection, reducing considerably risks related to systemic exposure [6].

This case is illustrative for the quick and long lasting analgesic effects we reported earlier in patients suffering from various painful neuropathic syndromes, treated by phenytoin 10% cream [5]. We selected to compound phenytoin in a cold cream base, due to its properties as a broad acting sodium channel blocker. Earlier we discussed three putative targets accessible by topical treatment via in the skin: the nociceptors, the keratinocytes and the immune-competent cells [6]. In all these cell populations, various sodium channels reside in the cell membranes.

In diabetes, it is increasingly recognized that methylglyoxal and Advanced Glycation End-Products (AGEs) contribute to the pathogenesis of neuropathic pain. The endogenously increased concentrations of methylglyoxal and AGEs are known to be associated with the development of neuropathic pain and other diabetic complications such as retinopathy, including pathological alterations of sodium channels [7,8] Methylglyoxal is a non-specific modulator of the arginine, cysteine, and lysine residues of selective intracellular proteins of sodium channels, such as the Nav 1.8 channel, playing a role in neuropathic pain [9]. These findings supported the selection of the broad acting sodium channel blocker as the pharmaco-active component in a topical formulation to treat peripheral neuropathic pain. As there is an alarming rise in the diagnosis of neuropathies caused by type 2 diabetes, new effective therapies with a safe profile for the treatment of peripheral neuropathic pain are needed [10]. A topical phenytoin formulation could be such new treatment.

Conflict of Interest

The author is one of the 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.

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