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Fibromyalgia as a Localized Non-Length-Dependent Small Fiber Neuropathy, Responding to Topical Phenytoin

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Abstract

A number of fibromyalgia patients were treated by prescribing a topical analgesic treatment based on phenytoin cream. This often resulted in clinical relevant pain reduction and increased quality of life. One explanation of this phenomenon could be that these patients are not suffering from fibromyalgia in a classic sense. In reality they might suffer from localized non-length-dependent small fiber neuropathy (NLDSFN). Recent studies suggest a prevalence of small fiber pathology in around 50% of all fibromyalgia patients. This would imply that half of all patients suffering from fibromyalgia might profit from a topical treatment based on the broad acting sodium channel blocker phenytoin.

Keywords: Neuropathic; Treatment; Formulation; Pain; SFN

Introduction

Small fiber neuropathy (SFN) is quite well recognized, and its diagnosis via a skin biopsy is an established procedure. Pain symptomology related to localized non-length-dependent small fiber neuropathy (NLDSFN) is much less known and might easily be mistaken for a conversion disorder [1].

We have recently described some patients suffering from wide-spread pain resembling fibromyalgia, responding positively on topical treatment with phenytoin cream, a broad acting sodium-channel blocker. This provoked us to suggest an ex juvantibus diagnosis of NLDSFN in fibromyalgia responders to the topical cream. [2] This means, that patients who respond favorably to the treatment with a topical formulation of phenytoin, are belonging to a homogenous cohort of patients with comparable etiopathogenetical characteristics. This characteristic would be pathology of the small fibers in the skin. Topical phenytoin does not cross the skin to enter the bloodstream and can therefore not act as an analgesic elsewhere in the nervous system, its mechanism of action must reside in the skin.

Fibromyalgia is a Localized Non-Length-Dependent Small Fiber Neuropathy

We have reported earlier a number of patients suffering from chronic pain, diagnosed as fibromyalgia patients elsewhere. One of our patients was a 63-year old female who was diagnosed with fibromyalgia more than 30 years ago [2]. She was treated with various analgesics

but only occasional bupivacaine hydrochloride injections in tender points could reduce the pain. After prescribing topical phenytoin 10% cream a clinical relevant pain reduction occurred. A second patient was a 52-year old woman suffering from chronic fibromyalgic pain during many years, leading to a totally inactive life. Many different analgesics where tried, but none helped. After starting treatment with topical phenytoin pain was greatly reduced and patient starting to look for a job, doing housework again and spoke of a 'new body and life'. A third patient was a 42 years-old female patient with a number of extra medical conditions including a spectrum of autoimmune disorders and rheumatoid arthritis. She subsequently developed fibromyalgia increasing in intensity with the onset of her other disorders. She was started on topical phenytoin 5% and then 10% which produced a remarkable contraction of the painful area around the tender points which occurred within a few days.

Some years ago, we selected topical phenytoin as a broad and long acting sodium channel blocker for the development of a compounded formulation. The oil in water formulation we selected was recently confirmed to be one of the best choices for formulating phenytoin as a topical delivery formulation by the Royal Dutch Society of Pharmacists [3]. In the Netherlands, many physicians prescribe phenytoin cream 10%, 15% and 20% for the treatment of localized peripheral neuropathic pain, for instance burning feet in small fiber neuropathy (SFN), diabetic neuropathy and chemotherapy induced polyneuropathy. The most frequent underlying cause of SFN has been identified as diabetes [4].

We tested safety and efficacy of topical phenytoin formulations in open and single blind studies, in a number of these peripheral neuropathic pain states. As we could not detect plasma levels after application of the cream, we argued the mechanism of action in peripheral neuropathic pain has to be intradermally [5-7]. Now the questions we can ask ourselves is: why would some fibromyalgia patients respond favorably on the application of a topical formulation containing phenytoin if the pathogenesis is located in the muscles, and phenytoin does not penetrate into the blood? [5]. The fact that some patients responded after the treatment with topical phenytoin suggests that the pathogenesis, at least in these cases, resides in the skin, and not in the muscles. And this suggest that under the header 'fibromyalgia' two different disorders reside, classical fibromyalgia and a variety based on small fiber pathology. This asks for a more differentiated approach in diagnosis and therapy than our current approach.

Fibromyalgia to date could be seen as one of the failures of medical science. Fibromyalgia has been aggressively investigated since Robert Froriep, mentor of Virchow was the first to describe tender, palpable hardening in muscles of patients with rheumatic disease in 1843. Like many disorders in medicine fibromyalgia has gone through various cycles of presumed etiology or etiopathogenesis, and it has sometimes even been labelled psychosomatic. First papers in PubMed covering topics related to fibromyalgia can be identified back to 1945. To date more than 10.000 papers contributed to our knowledge, but up to this day, we still do not have a definitive and effective treatment, neither do we understand fully its etiology and pathogenesis which help to understand this widespread pain syndrome.

In 1958 myofascial tender points and "Trigger Points" were discussed by Steinbrocker, et al. in relation to fibromyalgia as painful circumscribed points of maximal tenderness, while referred pain was produced when "trigger points" were stimulated or needled. Over the years, treating trigger points by local infiltration with anesthetics had a fair degree of success [8]. Such trigger point therapy however is only partially effective and temporary. Fibromyalgia may be related to a cycle of dysfunctions between the periphery and the central nervous control, and the question is, how can this cycle be broken? Perhaps the treatment with a topical formulation containing phenytoin might play a role here. If a significant number of fibromyalgia patients with positive trigger points actually suffer from a wide spread non-length dependent small fiber neuropathy, this indeed might become a therapeutic option. As has been emphasized in the past, a number if symptoms in fibromyalgia, such as trigger points, referred pain and pain associated with muscle spasm can be attributed to abnormal control mechanisms in a complex cybernetic system. The peripheral sensitization of pain small fibers might in that case be the drives of a chronic wind-up phenomena in the central nervous system [9].

Based on a number of experiments in the field of diabetic and other causes of peripheral neuropathies, while using topical 5-20% phenytoin cream, we highlighted in the recent past the pathogenetic importance of the small nerve fibers in the skin for a number of peripheral neuropathic pain disorders. Together with Professor Nicolette Notermans, from the

neuromuscular center of the Utrecht Academic Medical Hospital in the Netherlands, we reviewed the pathogenesis of a number of small fiber neuropathic pain states, and linked this pathogenesis to the analgesia seen in these patients after the application of topical phenytoin. We now suggest that a sub cohort of fibromyalgia patients might also qualify for the treatment with topical phenytoin [10]. It has been pointed out repeatedly in the recent past, that fibromyalgia has a number of neuropathic pain features, being a stimulus-independent pain state, accompanied by allodynia and paresthesias [2]. There is additional histological support for our hypothesis, and it was recently found that more than half of the patients presenting with neuropathic pain and who met diagnostic criteria for fibromyalgia, suffered from small fiber neuropathy, detected by skin biopsy testing [11]. The evidence for an involvement of small fibers in fibromyalgic pain is supported by many more recent findings [12]. Based on the assessment by corneal confocal bio-microscopy, women suffering from fibromyalgia were found to have thinner corneal stromal nerves and decreased corneal nerve plexus density when compared to healthy controls [13-19]. The corneal nerve atrophy was also found to be associated with neuropathic pain descriptors. In addition to this there is evidence of neurogenically derived inflammatory mechanisms in the peripheral tissues [19,20].

Recently a meta-analysis was conducted to answer the question of the prevalence of SFN in fibromyalgia patients. Eight studies were identified, and diagnosis was based on skin biopsy (6) and corneal confocal microscopy (2) - the estimated prevalence ranged between 30-76%, and a forest plot analysis showed an overall prevalence of SFP in fibromyalgia of 49%! [21].

Conclusion

If a significant cohort of fibromyalgia patients (around 50%) in essence suffers from a disturbance of the small fibers, new therapeutic inroads based on the treatment with topical formulations containing the broad acting sodium channel blocker phenytoin, could open a new window of opportunity for these patients. To date a specific treatment of pain in fibromyalgia is still missing, and many patients thus are treated by general analgesics, with troublesome tolerance and quite some systemic side-effects. Numbers needed to treat are disappointing and a new topical approach with phenytoin cream might be of use in a considerable cohort of fibromyalgia patients.

Conflicts of Interest

JMKH is the holders of two patents: topical phenytoin for use in the treatment of peripheral neuropathic pain and topical pharmaceutical composition containing phenytoin and a (co-) analgesic for the treatment of chronic pain.

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