Pain in Chemotherapy Induced Peripheral Neuropathy treated with topical phenytoin cream

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Abstract

Pain due chemotherapy induced peripheral neuropathy (CIPN) is difficult to treat, and to date there are no analgesics with a proven clinical relevant analgesic effect. In 2016 we started a topical phenytoin project and meanwhile we documented the efficacy and safety in 71 cases of patients suffering from peripheral neuropathic pain, treated with a special phenytoin 5% or 10% cream. We will present two cases from nine CIPN patients in our data pool collection of patients, responding well to application of the cream, though reporting a significant difference in duration of action. We also present a strategy to enhance duration of analgesia by making use of the boosting effect of combinations of analgesics in the same base cream.

Introduction

Pain due chemotherapy induced peripheral neuropathy (CIPN) is difficult to treat, and there are no analgesics with a proven clinical relevant analgesic effect. For instance, duloxetine, recently tested in a phase III study, only decreased pain compared to placebo with less than 1 point on the numerical rating scale (NRS: 0 is no pain, 10 is worst pain imaginable) [1].

To date, in our clinic we have treated a cohort of 71 patients suffering from neuropathic pain, which we all documented in great detail, using a topical cream formulation containing phenytoin in two different doses, 5% and 10%. Most of the patients were suffering from neuropathy induced by diabetes mellitus, chronic idiopathic axonal polyneuropathy (CIAP) and CIPN. Some other patients were suffering from post-herpetic neuralgia, trigeminal neuralgia, and pain due to nerve compression. Most patients reported clinical relevant pain reduction (reduction of at least 30%) and did not report any adverse events. The majority of patients suffering from peripheral neuropathic pain reported a reduction of pain of at least 50%. Nine patients suffered from CIPN. From these nine patients, we will present two patients, both responding quite favorably to a treatment of phenytoin 10% cream. Most patients experienced a pain reducing effect lasting for about 3 hours to 24 hours. However, these presented two patients experienced pain reduction after phenytoin 10% cream application of 4 days and only 2.5 hours. In cases like the second patient we mostly switch to a combination cream consisting of 10% phenytoin with 10% amitriptyline. We selected a special base to make such combinations feasible. The clinical endpoint selected for all these patients is the NRS for pain.

Case presentations

A 53-year-old female developed CIPN in both lower legs and feet due to the treatment of mama carcinoma with positive lymph nodes. She scored her pain intensity with a 9.5 on the NRS. The pain was characterized as painful cold, tingling, pins and needles. Her current medication was tamoxifen 20 mg once daily. An open response test with phenytoin 10% cream was performed. Phenytoin 10% cream reduced her pain from a score of 9.5 to 2 on the NRS 8 minutes after application of the cream. The duration of analgesic effect was nearly 3 days (around 70 hours). She did not report any side effects. The
The clinic in 1938 [5]. Phenytoin is the first modern anticonvulsant, introduced in phenytoin creams, as phenytoin also possesses anti-inflammatory and neuropathic pain triggered us to create phenytoin creams, as phenytoin also possesses anti-inflammation and neuropathic pain triggered us to create phenytoin. The combination of mild local neuro-inflammation might be one of the major mechanisms underlying CIPN [4]. The reciprocal cross-talk between the nervous and immune systems is suggested to contribute to the emergence of neuropathic pain during treatment with chemotherapeutics, and the low dose selected there were other flaws in this trial, we ruled out analgesia via central mechanisms: the level of phenytoin in the blood was below the threshold of detection. Meanwhile, we have documented 16 of such cases, all supporting a local mechanism of action, independent from systemic absorption transdermally.

Since this treatment she sleeps 6.5 till 7 hours each night in a row, without waking up due to pain. The frequency of electric shocks is also diminished with 20%, though the intensity remained the same. She can now walk longer: 30 minutes instead of 10 minutes. Average pain was reduced from a score of 8 to a 4.5 on the NRS.

Discussion

Chemotherapy induces toxic adverse effects to the peripheral nervous system and considerably reduce the quality of life. It is estimated that approximately 30% to 40% of patients treated with chemotherapy will develop CIPN [2]. Such adverse events often lead to a reduction of chemotherapy dosage or even in discontinuation of therapy. For the time being duloxetine is mentioned as the only analgesic capable of reducing these pains, the clinical effect however is small [3].

The reciprocal cross-talk between the nervous and immune systems is suggested to contribute to the emergence of neuropathic pain during treatment with chemotherapeutics, and neuro-inflammation might be one of the major mechanisms underlying CIPN [4]. The combination of mild local neuro-inflammation and neuropathic pain triggered us to create phenytoin creams, as phenytoin also possesses anti-inflammatory activity, first described in wound healing.

Phenytoin is the first modern anticonvulsant, introduced in the clinic in 1938 [5]. Meanwhile, it has been repositioned and repurposed for a number of indications, and neuropathic pain is the most recent indication [6]. Elsewhere, we have discussed the various mechanisms of action of topical phenytoin when applied on the skin of patients suffering from neuropathic pain. Its sodium channel blocking properties clearly contribute to its analgesic effect (see figure 1). One additional mechanism of action might be linked to the immunomodulatory role of phenytoin, which in the case of CIPN might contribute to the downregulation of peripheral inflammatory mechanisms in small nerve fibres in the epidermis. In the first patient we ruled out analgesia via central mechanisms: the level of phenytoin in the blood was below the threshold of detection. Meanwhile, we have documented 16 of such cases, all supporting a local mechanism of action, independent from systemic absorption transdermally.

Topical treatment of pain in CIPN using creams has been only rarely been documented [7, 8]. One pivotal phase III study evaluating a topical cream on the base of 2% ketamine plus 4% amitriptyline cream, but the selection of suboptimal doses did not lead to effective analgesia [9]. Another phase III trial evaluating the combination of ketamine 1.5%, amitriptyline 3% and baclofen 0.75% gel, resulted after 4 weeks only in a trend toward more improvement in sensory neuropathy and a statistically significant improvement in motor neuropathy as measured by the EORTC QLQ-CIPN20 [10]. Apart from the low dose selected there were other flaws in this trial, we discussed elsewhere [11]. We realized that the concentration of compound in analgesic creams needs to be as high as possible, without inducing local irritating effects, and prescribe since many years amitriptyline in 10% cream, ketamine in 10% cream and phenytoin 10% cream [12, 13].

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If we use combination of analgesics, we always select the same cream base, so that patients can combine various analgesics easily and rub these in on the painful areas, in various combinations. Based on the experiences and preferences of patients we selected a number of analgesics and co-analgesics and prepared compounded combination creams. Two of the most successful combinations are both based on phenytoin 10%, in the first combination we added amitriptyline 10% and in the second combination we combined with ketamine 10%. By doing so patients reported back that the duration of action could be prolonged considerably, making less applications daily possible.

Topical analgesia based on phenytoin creams seems to be a new modality of treatment of pain in CIPN. These preliminary findings will be followed up by findings based on placebo-controlled studies, starting with a number of n-of-1 crossover studies[14].

Conflict of interest

Authors 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 for the treatment of chronic pain.

References


