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Treatment of Painful Diabetic Neuropathy in Sub-Saharan Countries: Bottlenecks and Opportunity for the Repositioning of Phenytoin as a Topical Treatment

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Abstract

Treatment of Painful Diabetic Neuropathy (PDN) is still quite suboptimal. The use of many of the analgesics and co-analgesics recommended in most guidelines is complicated by issues as adverse events, low compliance and drug-drug interactions. Thus, the numbers needed to treat for most drugs in this field is relative high, while numbers needed to harm are low. This holds true for the western industrialized population, but definitely also for populations in Sub-Saharan Africa (SSA), as most of the analgesics of choice are not listed on the essential lists of these countries. Detailed data on the prevalence and incidence of PDN are also missing. It is estimated that PDN will increase considerably in the near future. Moreover, well controlled clinical trials evaluating the efficacy and safety of most currently used analgesics in these countries are extremely scarce if not absent. As the metabolism in the black population is known to be different from the white population, side-effects can vary and toxic metabolites might be induced in both populations in different frequencies, as has been demonstrated for opioids. Thus, there is a great need for new approaches in the treatment of PDN, and repositioning old drugs in new topical formulations might be of use. We will present the rationale to evaluate topical Phenytoin cream as a new treatment option in PDN, suitable for the SSA and present first steps related to a pilot trial in the Gambia.

Keywords: Repurposing; Development countries; Neuropathic; Gambia

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Introduction

Treatment of PDN in SSA is suboptimal, as many of the first and second choice drugs are not available for everyday practice. Moreover, due to frequent adverse events and weak efficacy many patients are not compliant with pharmacotherapy and thus a great percentage of patients remain suffering from PDN. Both issues of cost and effectiveness, as well as availability define the therapeutic landscape in this field. New therapies which are cheap, and have a low propensity for side-effects and drug-drug interactions are welcome. Drug repositioning or repurposing is increasingly recognized as important, especially also for health care systems in SSA, since old drugs are often quite cheap and might unexpectedly have positive therapeutic effects. However, to date most repositioning focus in SSA is on infectious diseases; we will build a case for repositioning a topical Phenytoin formulation in PDN, as pain is also increasingly recognized as a fruitful field for drug repositioning [1,2].

Epidemiology of PDN

Data on the prevalence of diabetes and neuropathy, as well as on diabetic neuropathy and painful diabetic neuropathy in Sub-Saharan Africa (SSA) are scare. There is however a clear understanding in all papers covering this topic since more than 50 years that the prevalence is high and rising in the entire area, and starts to become a health problem to be respected [3,4]. Already as early as 1974 it was pointed out that diabetic neuropathy is "*a disease of great frequency-perhaps greater than is generally appreciated*" [5]. The author estimated a prevalence of 30% of diabetic neuropathy in the diabetic population. It was also clear at that time that metabolic control of black diabetics needs much attention [6].

Prevalence of DM is rapidly growing with a disproportionate burden falling on low- and middle-income regions [7]. Painful diabetic peripheral neuropathy has been identified as one of the main causes of neuropathic pain in SSA elderly population [8].

In SSA DM prevalence is now as high as 18% in some countries and current estimates portend that the prevalence of DM in the region could nearly double by the year 2045, which means that

more than 40 million people would be living with diabetes in sub-Saharan Africa [9].

Access to regular health-care however remains limited for most populations in the sub-Saharan region [10-12].

Research to date on Distal Symmetric Polyneuropathies (DSP) in SSA has been focused primarily on HIV– associated polyneuropathies or toxic antiretroviral neuropathies. It is in general stipulated that there is only limited data on the epidemiological features of DSP in the region. Moreover, research in SSA is conducted in urban regions only [13].

Treatment of PDN

The local choice of medication is limited not only by the medical context, but also by cost and availability. Some of the medications usually prescribed for peripheral neuropathic pain such as gabapentin and pregabalin are relative expensive for use in field settings [14]. This might be one of the reasons why none of the first line recommended analgesics are listed on the WHO list of essential medicines [15]. Many National Essential Medicines Lists (NEMLs) however listed such medications, most referred to tricyclic antidepressants. Duloxetine and venlafaxine were infrequently listed, and the majority of NEMLs did not include a gabapentoid. Half the NEMLs listed tramadol, while morphine, carbamazepine and sodium valproate, were almost universally listed. Apparently only few NEMLs referred to the assessed drugs as relevant for the treatment of neuropathic pain. Around 1 in 10 NEMLs referred to amitriptyline and carbamazepine for treating neuropathic pain [16]. The conclusion of this analysis was that there was clearly a poor selection of recommended treatments, leading to a high likelihood of side-effects and a high number needed to treat (>4). In the 75% cases of a non-response to the initial treatment, no or only very limited alternative therapies are available. Further, even when recommended drugs are listed, the drugs generally are not indicated, or are inappropriately indicated, for the treatment of neuropathic pain.

The clinical overlaps between the neurological disturbances in PDN and of vitamin or micronutrient deficiencies are challenging. Vitamin B and micronutrient deficiencies seem to contribute to severity of symptoms in PDN, may lead to further irreversible neurological disability when causal treatment is suboptimal [17]. Although there are a few papers describing diabetic foot problems in SSA, reference to the treatment of neuropathic pain is missing [18].

In the everyday life situation in SSA, paracetamol, NSAIDs and opioids such as morphine, are sometimes prescribed for neuropathic pains, although the efficacy of those drugs in peripheral neuropathic pain is quite low.

Evaluations of analgesics as recommended in the various guidelines in black populations are however rare. This is an important issue, as the metabolism of analgesics in blacks might be different and result in higher concentration of toxic metabolites, leading to more intense adverse events, as was demonstrated in 2014 [19]. Already in the 80s of last century black people from Ghana and Kenya showed a different metabolism of paracetamol compared to white people from Scotland [20]. Biological and psycho-sociological factors related to chronic pain management between diverse racial populations are different and in general not taken into consideration [21,22].

Formal RCT's evaluating analgesics for neuropathic pain in Africa are difficult to find. A search in Pub Med based on the key words 'neuropathic', 'pain', and 'Africa' related to 'Clinical Trial' did not identify any RCT done in an African population.

Carbamazepine 200 mg three times per day was evaluated in the 70s in a small South African population following a double blind-cross-over RCT in 40 patients, with a total duration of treatment of 14 days only. It was reported that on days 10 and 14 differences between the placebo and carbamazepine were significant ($P<0.05$). In a paper in 1979 from the University of Cape Town and Groote Schuur Hospital, the recommendation was to direct management at maintaining or providing a pain-free foot, and the various aspects of neuropathic pain was discussed, no reference was made to any analgesic [23]. Clearly formal RCT's testing (co-)analgesics in peripheral neuropathic pain in the SSA population are missing, and there is a need to intensify the focus of clinical science to this field of severe neuropathic pain in diabetes.

Topical treatment of PDN via repositioned Phenytoin in SSA: a putative project

Phenytoin has been evaluated extensively in the past as an anti-neuropathic pain agent [24-26]. Evidence supporting its therapeutic effects in trigeminal neuralgia is as strong as evidence for the gold standard, carbamazepine [27]. In 2015 we started compounding Phenytoin in different concentrations in a base cream and treated various patients suffering from peripheral neuropathic pain conditions [28]. This was part of a new repositioning effort to develop the old anticonvulsant drug and unselective sodium channel blocker in a new indication [29-31]. Especially for the treatment of PDN there is a good rationale to treat with Phenytoin cream, as its mechanism of action is intricately connected to the pathogenesis of the burning pain [32,33]. Its action is intradermally, and in 15 of our patients tested Phenytoin blood levels were below the limit of detection [34]. Meanwhile we, together with other Dutch physicians, have treated over 100 patients with Phenytoin cream, and to date no serious adverse events have happened, neither did we see any indication for systemic exposure of Phenytoin.

Our patients tell us the action of onset was within 30 min after the application of the cream to the feet [35] and in order to objectify this, we developed a single-blind response test we published elsewhere in great detail [36]. We first developed an open response test, applying phenytoin cream on one foot and comparing to the pain as assessed for the untreated foot. In case of response we saw a fast response: a decrease of at least 2 points on the NRS within some 20 min to 30 min. We then added a placebo cream to the response test, applied on one foot, while phenytoin was applied to the other in a single blinded fashion. We defined as a responder: after 15 to 30 min, the patients needed to notice at least a difference of at least 2 points on the NRS in pain reduction between Phenytoin cream and the placebo cream. This single-blind response paradigm is easy to conduct, the effects start soon, while the patient is waiting in the waiting room, and after 30 min the physician can decide whether prescribing phenytoin cream is useful, as phenytoin -responders can then be identified. In this way, the chances are lower that we sent the patient home with a prescription for a cream while he is a non-responder. That would decrease the compliance and decrease the chances the patient will return for other treatment.

Repositioning phenytoin in a topical formulation for the treatment of PDN in SSA would have various advantages:

1. Phenytoin costs of good are low

2. Compounding phenytoin cream has been done successfully and instructions for compounding are simple

3. Patient response is evaluable within 30 min

4. Ease of administration, flexible dosing possible

5. No systemic side-effects, no drug-drug interactions

In order to evaluate the feasibility of 10% phenytoin cream in PDN in the Gambia we intent to start a pilot project in three phases in a small cohort of Gambian patients.

In order to first evaluate whether the project would be feasible we would recommend to start with a simple open case-collection of around 10-20 patients. The participating physicians could evaluate not only the cream in its safety itself, but also give feedback on the designed case records and scales as developed so far (see attachments). Basically, only demographic data and some data related to the pain intensity and duration as well as current medication will be monitored, as well as the results of the scoring on the DN-4 scale (recommended for Africa). No additional tests are required (no urine, blood, stool etc.).

If the project seems feasible, a second phase could be designed based on a single blind response test in those PDN patients with equal intense pain in both feet, and the patient itself is its control. Placebo cream is already available. Such single-blind study would only require patients to apply cream once on both feet, and the pain reduction read out would be available within 30 min 60 min after application. Estimation n=24 if this second step further supports the project, a full powered double-blind, placebo controlled RCT could follow.

Conclusion

Guidelines on the treatment of PDN in SSA are absent. Treatment options are few due to costs, and adverse events of cheaper analgesics such as amitriptyline lead to low compliance in patients, and many remain unresponsive to this drug. Diabetes PDN however is increasingly recognized as a rising health care problem. To date there is no clear answer on how to treat these pains neither is there any clinical trials evaluating cost-effective therapies in the SSA population.

Drug repositioning or repurposing is increasingly recognized as important, especially also for health care systems in SSA, since old drugs are often quite cheap and might unexpectedly have positive therapeutic effects. Phenytoin can be compounded in a topical cream, and to date no side effects have been dose-limiting. Furthermore, the onset of action seems fast, within 30 min.

We are currently in the phase of designing a pilot trial project in one of the SSA countries to evaluate the safety and efficacy of 10% phenytoin cream in patients.

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