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Extending the Therapeutic Scope for the Treatment of Neuropathic Pain with Topical Analgesics

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Commentary

Neuropathic pain is defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [1]. Peripheral nerve damage causes the release of pro-inflammatory mediators (including interleukin-1β, tumor necrosis factor-α, bradykinin, substance P, calcitonin gene-related peptide, nerve growth factor, and prostaglandins) contributing to the 'inflammatory soup'[2] The inflammatory response has adaptive functions enabling nerve repair [2]. On the other hand, these mediators have the undesired effect of sensitizing and stimulating nociceptors, leading to neuropathic pain [2]. The intensity of neuropathic pain progressively increases throughout the day [3]. This circadian cycle of neuropathic pain might be due to fluctuation of neurotransmitters and endocrine hormones, as well as repeated somatic stimulation and physical activity [3]. Allodynia (a potential characteristic of neuropathic pain) can exhibit temporal summation [3]. The fact that neuropathic pain often restricts walking and mobility, implies that physical activity evokes or exacerbates neuropathic pain [3]. Thus sensitization and stimulation of the peripheral nerve seem to play an important role in the aggravation throughout the day.

Neuropathic pain has a negative effect on quality of live, mood, sleep and work [4]. Around 90% of the patients do not receive adequate medication, such as antidepressants and anticonvulsants [5]. The reasons could be that 1) patients do not mention and/or qualify the bothersome sensations as pain, such as tingling, burning and painful cold, 2) physicians do not ask about the aspect of the pain and prescribe pain medication according to the World Health Organization analgesic ladder as used in nociceptive pain, such as acetaminophen and non-steroid anti-inflammatory drugs. These analgesics are not effective in neuropathic pain [6]. Antidepressants or anti-epileptics (calcium channel α_2-δ ligands) are the first choice for the treatment of neuropathic pain [7,8]. Unfortunately, after one year more than half of the patients receiving appropriate neuropathic pain medication is not compliant, which might be due to lack of effect or too much side effects [9]. Common side effects are sedation and drowsiness which affect quality of life [8]. Therefore, new other therapeutic options should be explored and developed.

One interesting therapeutic strategy is topical analgesia, especially for the treatment of localized neuropathic pain, defined as 'neuropathic pain confined to a specific area not larger than a letter-size piece of paper'. Approximately 60% of neuropathic pain patients had localized neuropathic pain [10]. Two topical analgesics are recommended in guidelines: lidocaine 5% patch as first-line treatment and topical capsaicine as second-line treatment [7]. Other topical analgesics in development are clonidine 0.1% gel, and the combination formula of amitriptyline 4% and ketamine 2% (Amiket) [11-13]. The advantages of topical analgesics is the fast onset of effect (within 30 minutes), nearly no systemic side effects when properly used, no drug interactions, and no influence on systemic drug metabolization [13]. Rarely, local side effects such as skin rash can occur. Multiple active compounds in topical analgesics seem to have a more pronounced effect, [14] most probably because targeting multiple receptors [13,15]. This assumption is in line with oral analgesics. Multiple analgesics give a more pronounced pain reduction, compared with single compounds [16,17]. Also higher concentration of the active compound seems to give better pain relief [13]. With regard to topical amitriptyline this compound is in most studies evaluated in combination with ketamine [13]. The maximum reported concentration of topical amitriptyline is 10% [13].

Due to the fast onset of topical analgesics, responders can be identified immediately. The circadian cycle and the aggravation of neuropathic pain with physical activity allows the patient to apply selectively, e.g. 30 minutes before a walk, or only in the evenings when the pain is more bothersome. Most patients apply topical analgesics 2 to 4 times daily. Systemic side effects might only occur when the patient is a poor metabolizer (~ 8% of the population) and/or applies the topical analgesic, such as topical amitriptyline, generously [13]. When systemic side effects occur, the patient is instructed to wait with application of the topical analgesic until disappearance of the side effects. Thereafter the patient has to apply less amount of the topical analgesic per application, and/or has to use a lower concentration of the active compound.

Generally, elderly patients develop neuropathic pain and usually have co-morbidities treated with polypharmacy. Thus this group of patients is prone to the increasing risk of side effects and drug interactions.

Therefore, due to the excellent safety and side effect profile, topical analgesics should be considered as a first-line treatment.

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