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Review Article

Repositioning Problems of Clonidine as Topical Formulation in Neuropathic Pain

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Abstract

Clonidine is an antihypertensive agent that has been repositioned in various formulations (epidural, oral, patch, gel) for neuropathic pain, though not without difficulties. In 1991, the first clonidine patch for neuropathic pain was developed and tested, and later on clonidine gel. There was support for clonidine as an analgesic drug based on anesthetic findings, when clonidine was administered intrathecally. However, only a few animal experiments supported its topical use, and arguments as to why clonidine would act peripherally were not very convincing. Based on the limited experience using clonidine patches in localized neuropathic pain, clonidine gel in the concentrations of 0.1% and 0.2% was developed. Without further explorations to assess the most optimal formulation, the efficacy of patch and gel remained debatable and the development was stopped in 2017 due to a failed phase IIb study in diabetic neuropathic pain. Various combinations between clonidine and (co-)analgesics were also tested, but those data remained anecdotal. In 1995 an early attempt was published to identify responders using an enrichment design, and the results indicated that a subpopulation of neuropathic pain patients might indeed benefit from the treatment with topical clonidine. As there was no follow-up for this enrichment approach, the question of whether topical clonidine is effective in the treatment of neuropathic pain still remains unanswered.

Keywords: *Transdermal; Drug Development; Formulations; Topiceuticals*

Introduction

The treatment of neuropathic pain poses a challenge for the clinician. The efficacy of all recommended analgesics in neuropathic pain is moderate at best, with numbers needed to treat between 3 and 10, and dose-limiting side effects are common. This implies that many patients will continue to suffer from pain, and new treatment modalities are therefore needed.

More and more old drugs are being recognized as potential treatments for new indications, which lead to the repositioning of such drugs. Clonidine is a good example of a drug, developed as an antihypertensive drug and repositioned as an anti-neuropathic pain drug. Clonidine has also been repositioned for other indications, such as acute alcohol withdrawal, akathisia, diarrhea, oral mucositis and prolonged surgical anesthesia. The repositioning in neuropathic pain however did not go smoothly due to a number of complications.

Topical analgesics, administered in patches or gels and creams, may have the advantage that the concentration of the active pharmaceutical ingredient (API) locally in the skin can become high, while the systemic drug levels remain low. However, this advantage will only be translated into pain reduction if the mechanism of action of the API resides in the skin and can be linked to the pathogenesis of pain. Furthermore, in order for the API to reach its target and lead to clinical relevant pain reduction, a number of additional requirements need

to be fulfilled, based on preclinical pharmaceutical and animal experiments. The most suitable animal model (usually rats) depends on the indication that is being developed [1]. In the field of the development of topical analgesics, the approaches selected are characterized by avoiding and omitting a number of key issues for success. This can lead to cumbersome results and haphazard findings.

A topical formulation containing a (co-)analgesic only leads to clinical relevant effects in neuropathic pain if we find answers on at least the following questions:

1. What is the target?
2. Where is the target?
3. How to reach the target?

What is the target?

Many APIs have different mechanisms of action, varying from sodium channels to N-methyl-D-aspartate (NMDA) receptors. The target selected should play a crucial role in the pathogenesis of the type of pain we want to treat. For instance, in pain states due to $Na_v1.7$ channel pathology, the affinity of the API for this subtype of ion channel needs to be high enough, and the compound needs to be selective. Not all targets described in literature lead to sufficient pain reduction due to the fact that networks of factors play a role, and some targets are just minor players in the field. The rationale behind the selection of the main target is therefore mandatory.

Where is the target?

Targets can be located in peripheral tissues (e.g. epidermis, dermis) and/or in the central nervous system (CNS). When targeting the CNS, sufficient blood levels of the API are needed to penetrate across the blood-brain barrier and reach the CNS target. When the target is peripheral such as the epidermis, specific formulations are needed in order to reach high concentrations of the API in the epidermis, with minimal or no detectable plasma levels. The rationale behind the selection of the formulation is therefore mandatory. Transdermal formulations (e.g. fentanyl patches) can deliver APIs for targets in the CNS, as well as peripheral targets such as the epidermis. Epidermal formulations are designed to reach the highest concentrations of API in the epidermis without reaching detectable plasma levels (e.g. lidocaine and capsaicin patches). Some transdermal formulations are developed to reach sufficient drug levels in the skin (capsaicin, lidocaine plasters).

How to reach the target?

If the main target is in the periphery, for instance complete peripheral neurons, sufficient blood levels are needed and thus a transdermal formulation is required leading to such levels. If the target is more of an epidermal nature (e.g. nerve endings), as it is in the case of capsaicin, other formulations are needed which do not lead to a deep penetration of the active compound in the skin.

In the analysis of the development of topical formulations of clonidine for the treatment of neuropathic pain, we will see that these simple key questions have not been answered adequately by the drug developers or by academia. Only after answering the first three questions can the last question be answered, of whether the selected formulation in a specific dose can sufficiently reduce neuropathic pain. The selection of the most appropriate patient group/indication is of course a key factor for success. To simply assess any API or clonidine containing topical formulation randomly in neuropathic pain related to diabetes or herpes zoster seems more a roulette approach than a rational approach.

What is the target?

Clonidine has been described as possessing analgesic properties since the 1970s [2,3]. Its mechanism of action was hypothesized to be centrally mediated, via central mono-aminergic and cholinergic mechanisms [4-6]. Lesions of the noradrenergic locus coeruleus raise nociceptive thresholds, and clonidine could also inhibit the firing of this locus [7]. These experiments led to testing the intravenous infusion of clonidine 2.5 µg/kg in humans as early as 1980. This dose lowered blood pressure but did not lead to analgesia of acute pain stimuli in healthy volunteers [8].

Epidural administration of clonidine, however, led in some situations to a mitigation of pain and step-by-step data was gathered supporting the analgesic effect of clonidine in centrally mediated pain syndromes [9]. Epidural clonidine was subsequently hypothesized to have a mode of action at the level of the dorsal horn of the spinal cord [10]. In a randomized double-blind study with 20 chronic pain patients, epidural morphine 5 mg in 5 ml of saline was compared with epidural clonidine 150 µg in the same volume. The reported analgesia was comparable in both groups, but the clonidine treated patients had clinically relevant drops in blood pressure (more than 20 mm Hg) leading to un-blinding [11]. Following the epidural administration of clonidine, the oral administration of clonidine was evaluated in pain in post herpetic neuralgia (PHN) in 1988 [12]. The rationale to conduct such a study was rather flimsy as it was based on epidural administration in other pain states. In a double-blind study with PHN 40 patients, the effects of clonidine 0.2 mg, codeine 120 mg, and ibuprofen 800 mg versus a placebo were observed. Only clonidine resulted in a statistical decrease of pain compared to the placebo (per-protocol analysis). No plasma levels were measured, and only the effects of a single dose during the first 8 hours after intake were evaluated.

Given the emergence of potential serious side effects, such as hypotension, rebound hypertension, and sedation, other ways to deliver clonidine were explored, such as topical formulations. A clonidine patch with a linear relationship between patch size and plasma concentrations was developed [13]. The first clinical study evaluating such topical formulation in a chronic pain syndrome was reported in 1991, and clonidine as transdermal patch was evaluated in six patients suffering from sympathetically maintained pain (SMP). Of these six patients, four were selected as putative responders, based on a positive sympathetic block in the past. By selecting a number of earlier findings, the authors hypothesized that SMP was a 'peripheral alpha-adrenergic receptor disease', suggesting that the topical application of an alpha-adrenergic blocking agent such as clonidine was rational. The analgesic effects in three patients were confined to the direct environment of the patch. The authors argued that the site of action was not likely in the CNS, but rather peripherally due to hypersensitization of alpha-1-adrenergic cutaneous nociceptors.

Where is the target?

Avoiding undesirable central side effects was not the only rationale for developing topical formulations. The main rationale given was related to the putative peripheral mechanism of action. Although the initial literature emphasized the central mechanism of action, a hypothesis for peripheral activity was generated based on the following two arguments:

1. Alpha-2 receptors are expressed by primary nociceptive sensory neurons [14].
2. Peripheral administration of alpha-2 receptor agonists leads to anti-nociception [15].

Based on these two arguments it was reasonable to hypothesize that topically administered clonidine could have anti-nociceptive effects [16]. The first argument however is not very convincing, as the study mentioned evaluated the effects of locally administered clonidine and noradrenaline at the level of the substantia gelatinosa (SG) neurons. The second argument was based only on circumstantial animal experiments and further development should perhaps have been postponed. As an example, we will discuss a paper from 2004, published in Pain [15]. In this study, topical clonidine was evaluated in an animal model of pain, the radiant heat tail-flick test. This test is not specific for neuropathic pain and thus its predictive value is low. Furthermore, there was no active control in this study, making the assessment of the magnitude of effect impossible. A dose-dependent analgesia emerged in the dose-range 20 to 75 mg/ml, but no plasma levels were detected in the study. Interestingly, the effects of topical clonidine could be inhibited by the systemic pretreatment with yohimbine, indicating a mechanism via the blood and peripheral alpha-2 receptors. The authors' conclusion that topically administered clonidine produces 'potent' (sic) anti-nociceptive effects without testing a reference compound thus seemed overly optimistic. Reference compound could be topically applied lidocaine 5%.

How to reach the target?

The first transdermal clonidine delivery system was developed to treat hypertension and clonidine was formulated in a patch [17]. These patches were subsequently used to treat localized neuropathic pain, for instance in 1991 it was reported that clonidine

administered via a transdermal patch relieved SMP under the patch [18]. However, such positive results were not always reproducible, and in a placebo-controlled cross-over study with diabetic neuropathic pain patients no clinical relevant pain reduction could be demonstrated [19].

Due to these mixed results, it was concluded that the dose of clonidine at the site treated needed to be higher than previously tested [20]. A gel was developed based on clonidine concentrations between 0.01 and 0.5%. The application of clonidine 0.1% gel led to plasma concentrations below or at the lower limit of those required for anti-hypertensive therapy. The development of clonidine patch and gel in all its ramifications will be a topic of a different paper.

Compounding pharmacists soon started to create other topical delivery systems containing clonidine, for instance to treat pains in the buccal cavity (in a concentration of 0.2 mg/g: 0.02%) or for PHN (150 µg/g: 0.015%) [21,22]. The low dose was probably selected in the light of oral resorption and potential severe side effects. Clonidine was also compounded in gels, in concentrations of 0.1% to 0.5%, alone or together with other (co-)analgesics, such as ketamine [23]. Various combinations have been tested in case series and human pain challenge paradigms [24-26]. Most of these studies evaluated doses around 0.1%, but studies combining clonidine 0.2% to 0.3% in compounded mixtures of (co-)analgesics have also been published [27-29].

Clinical trials evaluating topical clonidine: what is the preferred population?

In 1992 the first results of topical clonidine in painful diabetic neuropathy (PDN) were published [18]. However, the data gathered so far only supported the epidural administration of clonidine and was always accompanied by clinically relevant decreases in blood pressure. The unconvincing effects of pilot studies in PHN and SMP were quoted as indicators for exploring its effects in PDN. Step-by-step doses of 0.1, 0.2 or 0.3 mg/day given as a patch were evaluated against a placebo in a crossover design. In total, 27 patients entered the study of which 24 patients completed the study and were included in the evaluation. No plasma levels were monitored. This was surprising as the authors stated in the introduction that the tested transdermal dose form of clonidine yielded relatively steady blood levels. No statistically significant difference emerged.

The subsequently conducted clinical trials focused on only a few segments in the neuropathic pain spectrum, without any rationale to support the selection. We could identify only one rational approach, where the investigators tried to identify a responder population based on an enrichment design in 1995. Enrichment design of a trial is meant to include patients who respond to a treatment, not diluting the trial with non-responders and therefore reducing the number of trial patients to reach significance between the active and placebo group.

If you have splitters then you also have lumpers. Borgman (2000) tried to tie a number of syndromes together via a postulated unity of pathogenesis based on 'sympathetically maintained peripheral neuropathic pain syndromes': PHN, PDN and complex regional pain syndrome (CRPS). The lumping together presumably was driven by the patenting strategy of the author and was much less supported by scientific data.

In a randomized placebo-controlled study conducted by the group of Campbell (2012), clonidine 0.1% gel was tested in 179 PDN patients [30]. The total daily clonidine dose was 3.9 mg for 12 weeks. The study was negative, though a subpopulation (those patients who felt any aggravation of pain after capsaicin provocation) experienced statistically significant pain reduction compared to placebo. Campbell was the inventor of a clonidine gel patent that was filed in 2005 [31].

The Cochrane analysis of 2015 for topical clonidine in neuropathic pain included only two studies, with a total of 344 PDN patients, based on a randomized, double-blind design of at least two weeks' duration [32]. One study was the Campbell 2012 study, the other was reported in 2009 as abstract only [33]. Interestingly, both studies evaluated only one dose and formulation: clonidine 0.1% gel. Both studies were supported by the pharmaceutical industry producing the gel. According to the Cochrane analysis, the studies supported the conclusion that clonidine may provide some benefit in PDN.

Discussion and Conclusion

The development of a topical analgesic formulation for the treatment of neuropathic pain is based on a number of rational steps to generate sufficient and coherent data. These steps can be classified according to the classical drug development phases as preclinical and pharmaceutical steps and ultimately lead to well designed and conducted clinical trials in phases I, II and III.

As we discussed above, in both preclinical and pharmaceutical phases of the topical clonidine development a number of questions have not been adequately explored. These items of concern are summarized in tables 1 and 2.

Preclinical requirements in animal models	Results
Efficacy of formulation versus gold standard	Not available
Efficacy in relevant animal models for neuropathic pain	Not available
Efficacy related to plasma levels	Not available
Elucidation peripheral mechanism of action	Unclear
Dose-response curve	Established for clonidine solution
Relevant formulation tested	Not available

Table 1: *Preclinical requirements related to animal models.*

Pharmaceutical requirements	Results
Evaluation various topical formulations	Only patch and gel evaluated
Evaluation various strengths	Not available
Evaluation stability	Not available

Table 2: *Pharmaceutical requirements.*

In the absence of sufficient data generated during these two steps, the selection of patients for clinical studies in the field of neuropathic pain seemed overly naive. Only one study following an enrichment design addressed the importance of dissecting the correct population, in order for the optimal match between pathogenesis and mechanism of action. This approach however remained isolated.

For the future, for newly discovered APIs we recommend to first evaluate a specific formulation in adequate animal models for neuropathic pain and generate plasma data in the same models. Subsequently, a dose-response curve needs to be described and the drug under exploration in its optimal dose needs to be compared to the gold standard. Most importantly, before embarking on randomized clinical trials for discrete patient populations, enrichment studies need to be conducted to identify responder populations. In an era of individualized medicine, one should not lump together patients in one class (e.g. 'sympathetically maintained peripheral neuropathic pain syndromes') and expect one API to be active in such an undifferentiated patient group. As we previously analyzed for topical amitriptyline as well as in this case, the question of whether topically applied clonidine can reduce localized peripheral neuropathic pain has never been properly addressed [34].

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