

Topical Analgesics in Localized Neuropathic Pain: Transdermal Delivery or Intradermal?

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Some authors are convinced that topical applied analgesics act locally, as for instance E. Zur, who states in an extensive state of the art review on topical treatment of neuropathic pain using compounded medications the following: *"Topical drugs have multiple advantages: by definition, these drugs act locally on damaged or dysfunctional soft tissues or peripheral nerves."* [1] In this review, Zur introduces the term 'topical drugs', but such drugs do not exist. Drugs cannot be defined by the route of administration selected, and even drugs which are not lipophilic and therefore have a low propensity to penetrate the skin can be administered parenterally and will not act locally but systemically.

Drugs that can be applied on the skin in specific formulations can indeed act on various compartments of the skin and reduce pain. However, the difficulty is to rule out additional systemic mechanisms of action and sadly enough, in many studies on topical analgesics plasma levels have not been measured. Moreover, topically applied compounded analgesic creams have sometimes been compounded to lead to clinical relevant systemic absorption, as in transdermal formulations. The first topical amitriptyline cream was specifically compounded in pluronic lecithin organ gel (PLO) to induce plasma levels in the therapeutic range, and it was indeed successful. PLO was developed in the 1990s specifically to enhance the penetration of active pharmaceutical ingredients (APIs) through the skin. [2] The word 'topical' therefore does not relate to the place of action (via the targets in the skin), but merely implies that a formulation containing an API is applied on a localized part of our body, which indeed can be the skin. Clearly localized peripheral neuropathic pain therefore seems to be the ultimate indication for such topical applied analgesic.

We should therefore rephrase the question in the title to: "Topical analgesics in localized neuropathic pain: acting only on targets in the skin?"

In order for topical analgesics to act on targets in the skin alone, we would need to analyze two key issues: 1) the issue related to the efficacy, and 2) the issue related to the absence of systemic plasma levels of the API in the topical applied formulation. This rather rational approach is however often missing in the primary and secondary literature concerning topical analgesic formulations. For instance, in 2014 Branvold and Carvalho, both pharmacists with expertise in pharmaceutical compounding, mentioned the properties of topical formulations of NSAIDs, ketamine, baclofen, gabapentin and amitriptyline under the general header 'the benefits of compounded transdermal pain medication'. [3] Although the focus was on transdermal formulations, very little data presented were related to the plasma levels reached after the application of such formulations.

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They discussed 2 examples and only briefly referred to these: topical NSAID administration, which led to a maximal plasma concentration of less than 15% compared to oral NSAID administration, [4] and plasma concentrations of topical ketamine 10% PLO which were negligible when measured 1 hour after administration. [5] Now the fact that only small to very small and even undetectable plasma levels are the result of the application of transdermal formulations containing analgesics should create some doubt on whether we are indeed dealing with formulations designed to deliver sufficient amounts of a drug into the bloodstream via the transdermal route. The aim of a transdermal delivery system in essence is to deliver a sufficient amount of a drug to the body, and in the case of sub-therapeutic plasma levels, one looks for formulation improvements. For instance the initial transdermal delivery of naltrexone, based on a conventional formulation, yielded levels below detection but after applying a naltrexone patch with micro-needles, blood levels of naltrexone reached the therapeutic range. [6]

Transdermal delivery is characterized as a convenient and pain-free self-administration for patients, which eliminates the frequent dosing administration and plasma level peaks and valleys associated with oral dosing. Transdermal delivery can also substitute injections to maintain a constant drug concentration, and APIs with short half-life times can be delivered easily. [7] Evidently, one of the goals of transdermal delivery systems is to lead to therapeutic plasma levels. In the many papers published since the end of the last century on topical analgesics, data on plasma levels are often missing and we could not identify any paper that analyzed a dose range of a specific topical administered analgesic and correlated the efficacy and tolerability to the plasma levels measured. In fact, dose-range studies have not been found at all. For instance, for over half a century we know that adequate plasma levels of amitriptyline and nortriptyline must be between 60 to 220 ng/ml. [8] In literature on the topical administration of amitriptyline, levels measured are mostly a very small fraction of the required effective level, and quite often plasma levels are reported to be below the limit of detection. [9]

The argument put forward by Lynch, *et al.* that tricyclic antidepressants induce a peripherally mediated analgesia in preclinical models of neuropathic pain and that they may also be effective in alleviating neuropathic pain following topical administration actually appears a bit odd. They supported their argument via a study where amitriptyline was administered subcutaneously. Such a route of administration, however, could (and should) trigger a pain reducing mechanism situated under the skin, rather than in the skin. How would this support a topical mechanism if the formulation does not deliver amitriptyline transdermally? That remains a mystery. If topically applied analgesics acting via central and/or peripheral mechanisms are administered via those formulations said to be designed as transdermal ones, sufficient therapeutic plasma levels are needed. If the 'transdermal' formulations do not lead to measurable drug levels, these formulations are not transdermal formulations, even if based on PLO.

In our clinic we have monitored the clinical responses of more than 80 patients suffering from neuropathic pain on topical high dose phenytoin 10% cream, and have measured the plasma levels around 2 to 3 hours after application in 16 patients. In all cases the plasma levels were below the limit of detection. Most of these patients reported clinical relevant analgesia, with an onset of action around 20 minutes and a duration of 6 to 24 hours. The studies conducted by Lynch *et al.* on the combination of ketamine and amitriptyline in a topical formulation containing amongst others transcutol, a surfactant and penetration enhancer, did not lead to clinical effective plasma levels of both APIs, and the studies completed so far also have not convincingly been proven effective in localized neuropathic pain states. [9] Dose-finding studies were not conducted and the selected dose was quite low; in follow up studies the concentration was between 2% to 4% amitriptyline and 1% to 2% ketamine cream. [10-12] In our clinic we selected a 10% cream for both compounds. [12] Moreover, we did not make use of PLO or penetration enhancers such as DMSO in developing these creams because we did not aim for transdermal delivery.

On the contrary, we wanted to create a high dose in the epidermal tissue only. As we discussed elsewhere, 3 different tissue components in the epidermis cross-talk and contribute to pain signals: the nociceptors, the immune-competent cells, and the keratinocytes. [13] If we can downregulate the activity of these 3 components, for instance with a broad acting sodium channel blocker such as phenytoin, patients suffering from localized peripheral neuropathic pain could indeed profit. To evaluate topical analgesics, it seems discussing how to select the most appropriate patient groups is neglected. Based on our preliminary studies in various patient groups, we feel that

those patients who suffer from pathology residing in skin compartments can benefit in particular. They may also be suffering from small fiber neuropathic pain or pain in diabetic neuropathy.[14,15]

Based on this line of thought, it seems to us that to the question, "Topical analgesics in localized neuropathic pain: transdermal delivery or intradermal?" the answer will be: 'intradermal'.

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.

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