Topical Analgesic Formulations: Following the Transdermal Treatment Paradigm Only?

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Abstract

Topical analgesics are regarded as new inroads to treat peripheral neuropathic pain, with a number of advantages over oral treatments. Topical treatment reduces systemic induced side-effects and have good tolerability, without problems of misuse or abuse, or dependency. Furthermore, the onset of action is fast, mostly within 30 minutes. The mechanism of action of topical analgesics is either via transdermal delivery of the analgesic, or via intradermal mechanisms of action. In the latter case, plasma levels of analgesics in the blood are absent or very low. This perspective is missing in the approach of the ad hoc committee of the National Academies of Sciences, Engineering, and Medicine in the USA, installed by the FDA. In this short commentary, we plead for a more comprehensive approach of topical analgesics, including those formulations which explicitly are not based on transdermal penetration of the active pharmaceutical ingredient, but on intradermal mechanisms of action.

Keywords

Analgesia; Pain; Treatment; Formulations; Anesthesia; Pharmaceutical

Introduction

In 2019, sponsored by the U.S. Food and Drug Administration, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine in the USA started to conduct a study of the ingredients used in compounded topical pain creams [1]. The activity of this committee was defined at its website as: ‘Assessment of the Available Scientific Data Regarding the Safety and Effectiveness of Ingredients Used in Compounded Topical Pain...
Creams’. Especially in the USA, with a mounting resistance against opioids, new inroads of treating pain are sought. The committee defined its task as

1. To identify and analyze the scientific data relating to the ingredients used in compounded topical pain creams, and

2. To evaluate how those data translate to the safety and effectiveness of compounded topical pain creams with various combinations of those ingredients.

This seems important, since more and more pharmacists are active in this field, and various combinations of active pharmaceutical ingredients are used, not always based on a good rationale. For instance, in the past we discussed the absence of any rationale for compounding gabapentin in a topical cream, if the cream would not give rise to sufficient plasma levels. Gabapentin has its mode of action purely in the central nervous system, and definitely not in the peripheral nervous system residing in the skin. On the contrary, there is much rationale to compound a broad acting sodium channel blocker such as phenytoin or amitriptyline in a topical cream. Especially since the peripheral nociceptors as well as the keratinocytes are rich in sodium channels.

Interestingly the latter perspective of an intradermal mode of action has not been taken up by the committee, as they announced to comment amongst others on the level of benefit expected for the various ingredients given their likelihood of absorption through the skin.

This bias that topical administered analgesics need to be absorbed by the skin is based on the first ideas on topical analgesia and anesthesia, defined around half a century ago. In order to understand better the foundation of this bias we herewith review some of the older literature, especially related to some of the first patents in this field.

**Topical Anesthetics and Lidocaine Plasters**

Topical anesthetics such as benzocaine anesthetic solutions can be found already in the patent literature around the 50 of last century, and anesthetic patches for topical treatment have been described since 1964 [2,3].

The first anesthetic patch, based on 30% lidocaine, was said by the investigators to have the properties of an ideal anesthetic for the intact skin: effectiveness on topical application to the skin, abolition of pain, and adequate duration of analgesia [4]. The general idea of the plasters as worded in various patents is to deliver active compound via a transdermal formulation, sometimes referred to as a controlled release therapeutic system, to the body via the skin [5]. In a more recent patent on such technology, dated from 1991, ‘External preparation for application to the skin containing lidocaine’ blood level of lidocaine reached a constant level six to eight hours after the administration of the drug in a plaster, and the level was maintained until 24 hours after the administration, showing higher blood level than that of other comparative preparations, such as ointments (Figure 1) [6].
Figure 1: Mean blood level with the passage of time in case of the preparations of Examples 1 to 5, consisting of lidocaine plasters which comprises a drug-retaining adhesive gel base layer placed on a plaster, an and 1 to 10% by weight of lidocaine in the gel, in comparison with the lidocaine containing ointment of Comparative Example 1 and the plasters of Comparative Examples 2 and 3. (Adapted from Patent, owned by Teikoku Seiyaku Kabushiki Kaisha (1991): External preparation for application to the skin containing lidocaine. US 5827529 A).

Clearly for such plasters the topical formulation implies a transdermal technology, to reach adequate biological active plasma levels of the active pharmaceutical product (API).

‘The search for more effective topical analgesic agents than those known at present is a never-ending one’, we read in an old patent, priority date in 1957 [7]. However, in the case of the topical analgesics used at that time the author complaints about the lack of rapid penetration of the active pain relieving ingredients, which delays the desired relief. His invention was supposed to be a topical analgesic composition having rapid tissue penetrating powers to bring about increased effectiveness for the relief of pain. The invention was a combination of active pharmaceutical ingredients (API’s) such as ethylamine salicylates, an alkyl ester of amino benzoic acid and the antibacterial chlorinated phenol. Topical salicylates were mentioned more often as analgesic compositions, for instance in a patent (priority date 1960), based on choline salicylate dispersed in an ointment base to be used topically [8]. The inventors stipulated the fact that such topical formulation caused a rapid absorption into the blood stream through the skin to provide the desirable therapeutic clinical effect. Ten minutes after the topical administration of 10 ml. of choline salicylate the mean salicylate blood level was clearly measurable, and that a peak plasma level was reached in thirty minutes. In the 60s
a patent on DMSO claimed that it may be applied topically, for instance as an analgesic, to the intact skin or mucous membrane to achieve highly unusual rapid absorption to the affected sites in the body [9].

**Discussion**

In the above quoted patent literature we see the rise of the foundation of our thinking related to topical applied analgesics. Basically, one could state that in these primary sources quoted, topical application was nothing more than a dermal controlled release formulation of certain APIs. The choice of DMSO as a constituent of topical formulations further show the focus on reaching effective plasma levels of the compounded API. The same holds true for the choice of PLO as a vehicle for topical analgesics, PLO has been developed specifically as a vehicle improving absorption of APIs through the skin [10].

Since some years now, it became clear that there is a complex platform of interactive cells in the epidermis itself, participating in the process of peripheral sensitization. We discussed the importance of the main players in detail elsewhere, the nociceptors, the keratinocytes and the immune competent cells [11].

The newly installed committee in the USA should perhaps therefore not only focus on transdermal topical agents, but also on formulations developed to bring an API into the skin, while preventing the rise of therapeutically active plasma levels. If the mode of action resides in the epidermis, one could avoid systemic side effects with such a formulation. We developed a topical phenytoin formulation, and in the presence of analgesic effects we could not identify plasma levels of phenytoin, suggesting a topical and no transdermal mode of action [12].

**Conflicts of Interest**

The author is one of the patent holders of two patents related to the topical formulations of phenytoin in the treatment of pain:

- Topical phenytoin for the use in the treatment of peripheral neuropathic pain, and
- Topical pharmaceutical composition containing phenytoin and a (co-)analgesic for the treatment of chronic pain.

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