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Topical Analgesics: Critical Issues Related to Formulation and Concentration

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Abstract

Topical analgesics are in need to be differentiated from transdermal formulations of analgesics. Topical analgesics are characterized by local analgesic effects in the absence of systemic effects, and do not require a transdermal delivery formulation. There are two key issues in the development of topical analgesics. 1. For optimal clinical effects specific characteristics for the vehicle (a cream base or gel base) are required, depending on the physicochemical characteristics of the pharmaceutical active ingredient in the carrier. 2. One cannot and should not skip well designed phase II dose-finding studies, and this unfortunately happens often, as we will discuss in this paper.

In fact, we will demonstrate underdosing is one of the major hurdles to detect meaningful and statistically relevant clinical effects of topical analgesics. In the case of gels or creams containing ketamine, amitriptyline and baclofen, the dose-finding most probably needs to start at 10% for ketamine and amitriptyline and 2.5% for baclofen, while the doses tested were much lower: 4%, 2% and 1% respectively. Topical analgesics are promising inroads for the treatment of neuropathic pain, once sufficient attention is given to aspects such as formulation and concentration.

Keywords: Topical analgesics; Cream; Gel; Dose-finding; Formulation; Ketamine; Amitriptyline; Baclofen

Introduction

Topical pain treatments in the form of analgesic creams or gels are gaining more interest and such treatments may have a number of advantages over the classical oral administration of analgesics, such as:

- Local application only on the pain area where relief is needed
- Absence of systemic side effects
- Higher concentration of the analgesic at the pain area
- Fast onset of action
- low or no systemic drug levels
- Absence of drug-drug interactions, improvement of compliance, and no risk of dependency or abuse.

Furthermore, such topical formulations of analgesics and co-analgesics can easily be combined with any other formulation, orally or parenterally delivered, in order to enhance analgesia. Topical formulations therefore can become useful components of multimodel treatment of chronic and neuropathic pain.

The involvement of peripheral mechanisms in the skin has been suggested to be one argument for the use of topical approaches in the treatment of neuropathic pain [1]. The use of capsaicin and lidocaine in neuropathic pain, indicates that targeting such peripheral mechanisms indeed results in pain relief [2,3]. Insight in the complex interactions between nociceptors, immune competent cells, and epithelial cells further supports the use and evaluation of topical formulations targeting these 3 components [4,5]. As there is a multitude of pharmacological targets related to these components, it is perhaps naive to consider topical treatment by applying a topical formulation containing one active compound only. Nevertheless, some case studies and clinical trials already supported the efficacy and safety of such creams or gels, and we will discuss for the sake of simplicity in this paper only creams containing ketamine, amitriptyline and/or baclofen. Conflicting results have been reported, and we will bring forth a number of critical drug development issues not often considered in clinical trials published so far. There are two main topics we would like to address: formulation issues and concentration issues.

Formulation issues

In the literature on topical application of active pharmaceutical ingredients, such as ketamine, amitriptyline and baclofen, only rarely aspects related to the selected formulation are described in such detail that it becomes useful if one would like to duplicate the findings or reproduce the topical formulation. Recipes of the selected cream or gel-base are mostly not included. However, there are exceptions. An example of a useful description was published for a 5% ketamine gel: soybean lecithin granules (250 g; Spectrum LE 102) were mixed with 150 ml isopropyl palmitate. The mixture was stirred at least 12 hours until a uniformly dark, amber-colored solution was obtained. Ketamine (10 ml; Ketalar, 50 mg/ml) was added to reach a final concentration of 5 mg ketamine/ml gel [6]. The rationale why this gel formulation was selected however was not given by the authors. It might be because such a lecithin organogel has physicochemical properties enabling to dissolve all types of molecules: lipophilic, hydrophilic, and amphoteric. Lecithin gels are in general regarded as good carriers for transdermal transport of drugs [7]. It is an open question whether it was indeed the intention of the authors to create such transdermal delivery system for ketamine. Furthermore, no information was given on stability and pH of the selected organogel. The effects in responders were reported to occur within days. No plasma levels were taken.

Mahoney et al. pointed out that blocking NMDA and AMPA receptors peripherally limits pain in neuropathy and thus ketamine seems a good choice for topical application. They indicated that since NMDA receptors are found in the periphery, topical medications applied over the trigger site(s) of pain may decrease the neuropathic pain caused by peripheral and central sensitization [8]. In a placebo controlled cream study 17 patients entered and were randomly divided into either the treatment 5% ketamine cream or placebo cream. The gel was based on Aquaphor gel and was compounded into a cream. Further details, pH, stability were not given. Neither was there any explanation why this base was selected. The effect of placebo was as robust as that of the cream.

In a recently reported phase III study in 462 patients, to evaluate the efficacy and safety of a 2% ketamine plus 4% amitriptyline cream (KA cream) for reducing chemotherapy-induced peripheral neuropathy symptoms no details were given at all, no information on the cream base, neither a rationale for the selected dose [9]. Without discussing the formulation issues, the authors came to the conclusion that topical formulations containing amitriptyline together with ketamine are not recommended for reducing chemotherapy-induced peripheral neuropathy symptoms. This is an example of jumping to conclusions which we do not share, as we will discuss hereunder.

A comparable study in the same patient population (n=203) analyzed the efficacy and safety of baclofen 1%, amitriptyline 4% mg, and ketamine 2% in a pluronic lecithin organogel (BAK-PLO) versus placebo. In the publication 1 year stability data of the gel was give, but no rationale for the choice of the pluronic lecithin organogel neither a detailed composition [10]. There were however clear indications that the selected gel was not optimal: patients had difficulty working with the gel and getting it to absorb into their skin. This led the investigators to state that future studies should consider using a different liposomal transdermal base, which may be easier for participants to rub into their skin. The issue of the role of transdermal absorption however, versus topical application was not further discussed, although in a small subgroup of patient's balcofen and amitriptyline levels were low but measurable.

Clearly in none of the studies the authors brought forward a thorough line of arguments supported the choice of the vehicle. In most cases a base-gel was selected, although there have been indications that such a gel leads to patient compliance issues and to reduced convenience applying the gel. No pilot trials have been published were different vehicles have been compared.

Concentration issues

In clinical drug development it is often tried to shortcut development and avoid full powered dose-finding phase II trial designs, even by experienced colleagues from the pharmaceutical industry. This is especially the case in the development of topical creams and gels, most probably because in these field trials are not initiated and coordinated by robust pharmaceutical companies. Shortcuts however always end in tears, because the results are inconclusive or because one reads too much in the results and enters phase III without actually a good rationale or proof of principle. In the above discussed development of the KA and the BAK formulation one can find many of these drug development mistakes. The selection of a gel containing 2% ketamine and 4% amitriptyline, with or without 1% of baclofen has not been backed up by sufficient phase II data. In fact in the study on the BAK cream the Food and Drug Administration had specified the doses of the agents that were approved to be used in this study, and defined a dose lower than initially proposed, due to the lack of data on systemic absorption of this triple combination. Instead of implementing a small trial in order to evaluate the systemic absorption of the triple combination, the authors followed the FDA specification for dose, although they had to know that most probably there was no sufficient clinical data available to back up the dose selection. Logically, by selecting a low dose for all active components the trial runs a great risk to identify the no effect level only and end as a negative study. This was quite an expensive experiment leading to a new working hypothesis brought forward by the authors: next time selects a higher dose. This insight actually should have been clear from the beginning of the study.

A higher dose might indeed have led to a better clinical effect. Such a result has been documented earlier in the studying the effects of topical ketamine 10% in allodynia in CRPS patients in a double-blind cross placebo-controlled trial in 20 patients [11]. Ketamine reduced the allodynia significantly. Plasma levels of ketamine and its active metabolite, norketamine, were below the limits of detection after the creams were applied.

Conclusion

In a previous article I pointed out that topical analgesics need to be differentiated from transdermal formulations of analgesics [12]. Topical analgesics are characterized by local analgesic effects in the absence of systemic effects, and therefore a transdermal delivery form, such as liposomes of an organogel is not required. However, for optimal clinical effects specific characteristics of the topical vehicle (a cream or gel) are required. In order to test the efficacy and safety of an active pharmaceutical ingredient, such as amitriptyline, ketamine or baclofen one needs to compare the suitability of the selected vehicle in well-designed pilot trials. Furthermore, one cannot skip well designed phase II studies in order to specifically define the active concentration range of the selected topical and the lowest effect dose. Such phase II studies need to be well powered and this rarely happens. Most pilot studies are only suited for feasibility testing, whether one can find patients for inclusion, and whether the selected vehicle is acceptable and convenient for patients to 'smear'. In the previous article I introduced a new design for testing formulation and concentration issues in such a way that one can reduce the risk of completing a negative dose-finding studie. Using a simple phase IIa test design in a limited group off patients (blinded placebo or comparator controlled cross-over n=1 testing) we could, together with the patient, quickly test the pain relief of various formulations and concentrations, compare and select the best.

Topical analgesics are promising inroads for the treatment of neuropathic pain, but more attention to aspects such as the correct selection of the formulation and the concentration of the active pharmaceutical ingredient is needed.

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